25 June 2015
EMA/CHMP/285991/2015
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Perjeta

International non-proprietary name: pertuzumab

Procedure No. EMEA/H/C/002547/II/0010

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Table of contents

List of abbreviations

AE	Adverse event
ADR	Adverse Drug Reaction
AEGT	Adverse event group term
ALAT	Alanine aminotransferase
ASAT	Aspartate aminotransferase
ATA	Anti-therapeutic antibodies
AUC	Area under the concentration curve
BC	Breast cancer
BCS	Breast conserving surgery
bpCR	breast pathologic complete response
CA125	Cancer antigen 125
CarboG	Carboplatin and gemcitabine
CarboP	Carboplatin and paclitaxel
CHF	Congestive heart failure
CI	Confidence interval
CLEOPATRA	Clinical evaluation of pertuzumab and trastuzumab (WO20698/TOC4129g)
CMF	Cyclophosphamide/methotrexate/5-fluorouracil
CRC	Cardiac Review Committee
CRPC	Castration-resistant prostate cancer
CSR	Clinical study report
D	Docetaxel
DDI	Drug-drug interaction
DFS	Disease-free survival
DIBD	Development International Birth Date
DLP	Data lock point
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
ECOG PS	Eastern Cooperative Oncology Group Performance Status
eCRF	Electronic Case Report Form
EGFR	Epidermal growth factor receptor
EU	European Union
5-FU	5-Fluorouracil
FEC	Fluorouracil, epirubicin and cyclophosphamide
FEC/Ptz+T+D	FEC, q3w, for three cycles, followed by pertuzumab, trastuzumab and docetaxel, q3w, for three cycles
FISH	Fluorescence in situ hybridization
GD	Gestation day
GGT	Gamma glutamyltransferase
HER	Human epidermal growth factor receptor
HR	Hazard ratio
HRPC	Hormone-resistant prostate cancer
IBC	Inflammatory breast cancer
ICH	International Conference on Harmonization
IBD	International Birth Date
IHC	ImmunoHistoChemistry
iDFS	Invasive disease-free survival
IGF1-R	Insulin-like growth factor 1 receptor
IgG	Immunoglobulin G

ILD	Interstitial lung disease
IMP	Investigational medicinal product
INR	International Normalized Ratio
IV	Intravenous
LABC	Locally-advanced breast cancer
LR	Locally recurrent
LVD	Left ventricular dysfunction
LVEF	Left ventricular ejection fraction
LVSD	Left ventricular systolic dysfunction
MBC	Metastatic breast cancer
MedDRA	Medical Dictionary for Regulatory Activities
mRNA	Messenger ribonucleic acid
MUGA	Multigated acquisition
NCI-CTCAE (v3)	National Cancer Institute – Common Terminology Criteria for Adverse Events (version 3.0, 12 Dec 2003)
NEOSPHERE	Neoadjuvant Study of Pertuzumab with Herceptin in an Early Regimen Evaluation (WO20697)
NSCLC	Non-small cell lung cancer
NYHA	New York Heart Association
OS	Overall survival
pCR	Pathological complete response
PD	Progressive disease/disease progression
PFS	Progression-free survival
PK	Pharmacokinetics
Pla	Placebo
Pla+T+D	Placebo + Trastuzumab + Docetaxel
PT	MedDRA Preferred term
Ptz	Pertuzumab
Ptz+D	Pertuzumab plus docetaxel
Ptz+T	Pertuzumab plus trastuzumab
Ptz+T+D	Pertuzumab + Trastuzumab + Docetaxel
Ptz+TCH	Pertuzumab and TCH (docetaxel [Taxotere], carboplatin and trastuzumab [Herceptin], q3w, for six cycles
Ptz+T+FEC/Ptz+T+D	Pertuzumab, trastuzumab plus FEC, q3w, for three cycles, followed by pertuzumab, trastuzumab and docetaxel, q3w, for three cycles
q3w	Every 3 weeks
qRT-PCR	Quantitative Reverse transcription polymerase chain reaction
RECIST	Response Evaluation Criteria in Solid Tumors
rhuMAb	Recombinant human monoclonal antibody
ROW	Rest of the world
SAE	Serious adverse event
SCS	Summary of Clinical Safety
SMQ	Standardized MedDRA query
SOC	System organ class
T	Trastuzumab
T+D	Trastuzumab + Docetaxel
TCH	Docetaxel (Taxotere), carboplatin and trastuzumab (Herceptin)
TRYPHAENA	Tolerability of pertuzumab, Herceptin and Anthracyclines in Neoadjuvant Breast Cancer (BO22280)
TTP	Time to tumor progression
ULN	Upper limit of normal
US	United States (of America)

VTE	Venous thromboembolic event
WBC	White blood cell

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Roche Registration Ltd submitted to the European Medicines Agency on 1 September 2014 an application for a variation.

This application concerns the following medicinal product:

Centrally authorised Medicinal product(s): **For presentations: See Annex A**	**International non-proprietary name:**
Perjeta	pertuzumab

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II and IIIB

Extension of indication to include the use of pertuzumab in combination with trastuzumab and chemotherapy for the neoadjuvant treatment of adult patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer at high risk of recurrence.

As a consequence, update of sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2 of the SmPC. In addition, the MAH took the opportunity to make a correction in sections 2 and 6.6 of the SmPC regarding the dose contained in 1 ml of solution after dilution.

The Package Leaflet is updated in accordance.

The requested variation proposed amendments to the SmPC, Annex II, and Package Leaflet.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included EMA Decision CW/1/2011 on the granting of a class waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice / Protocol assistance

The applicant did not seek scientific advice/Protocol Assistance at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:

Rapporteur: Christian Schneider Co-Rapporteur: Daniela Melchiorri

Timetable	Actual dates
Submission date	01 September 2014
Start of procedure:	19 September 2014
Rapporteur's preliminary assessment report circulated on:	10 November 2014
Co-Rapporteur's preliminary assessment report circulated on:	12 November 2014
PRAC Rapporteur's preliminary assessment report circulated on:	19 November 2014
PRAC Rapporteur's updated assessment report circulated on:	28 November 2014
PRAC Rapporteur's assessment report endorsed by PRAC on:	04 December 2014
Joint Rapporteur's updated assessment report circulated on:	12 December 2014
Request for supplementary information and extension of timetable adopted by the CHMP on:	18 December 2014
MAH's responses submitted to the CHMP on:	18 March 2015
PRAC Rapporteur's preliminary assessment report on the MAH's responses circulated on:	21 April 2015
Rapporteur's preliminary assessment report on the MAH's responses circulated on:	22 April 2015
PRAC Rapporteur's assessment report endorsed by PRAC on:	07 May 2015
An Oral explanation took place on:	19 May 2015
2nd Request for supplementary information and extension of timetable adopted by the CHMP on:	21 May 2015
Rapporteur's preliminary assessment report on the MAH's responses circulated on:	02 June 2015
CHMP opinion:	25 June 2015

2. Scientific discussion

2.1. Introduction

Problem statement

Breast cancer is the most common form of malignancy in women, with an estimated 1.67 million new cases diagnosed in 2012 in the world. Breast cancer ranks as the fifth cause of death from cancer overall (522,000 deaths worldwide, 143,000 deaths in Europe) (Globocan, 2012).

Most breast cancers in the Western world (around 94%-95% of breast cancer patients in the US and Europe) are diagnosed when the cancer is still confined to the breast, with or without loco-regional lymph node spread (Howlader et al, 2011; Sant et al, 2003), and referred to as early breast cancer (EBC). At this stage, the disease is usually operable and can be treated surgically with curative intent. However, the disease can also be inoperable. Primary inoperable breast cancer includes locally advanced and inflammatory breast cancer.

Locally advanced breast cancer (LABC) describes a subset of invasive breast cancer where the initial clinical and radiographic evaluation documents advanced disease confined to the breast and regional lymph nodes. LABC occurs at first presentation in about one-fifth of breast cancer patients worldwide, with lower incidence in countries with established screening programmes but as high as 60% in some other countries (El Saghir NS et al, 2011). Usually, the definition of LABC includes large 'operable' primary breast tumours (stage IIB, IIIA) and/or those involving the skin or chest wall and/or those with extensive lymphadenopathies (stage IIIB, IIIC) (Macdonald SM et al., 2011).

Inoperable LABC is a heterogeneous designation encompassing a range of clinical situations from neglected low-grade Estrogen Receptor (ER)-positive breast cancers to rapidly progressing usually ER-negative disease (ESO-ESMO 2nd international consensus guidelines for advanced breast cancer (ABC2), 2014). A more homogenous form of LABC is inflammatory breast cancer (IBC) which has a distinct clinical and pathological course. IBC is a subtype characterised by erythema and oedema of a third or more of the skin of the breast with a palpable border, and an aggressive clinical course (European Society for Medical Oncology (ESMO) Clinical Recommendations, 2013). Inflammatory breast cancer is always considered stage T4 disease (T4d) (Tumour-node-metastases (TNM) staging system). Patients with IBC have an even worse prognosis than women with LABC. Median survival for women with IBC at diagnosis is around 2.9 years, compared with 6.4 years for women with LABC and > 10 years for patients with other non-T4 breast cancers (Hance et al, 2005). Inflammatory breast cancers are more frequently human epidermal growth factor receptor 2 (HER2)-positive than other breast cancer types (Charafe-Jauffret et al, 2004; Zell et al, 2009).

HER2 is involved in regulating cell growth, survival and differentiation (Sundaresan et al, 1999). Amplification and/or overexpression of HER2 occurs in around 15% to 20% of breast cancers (Wolff et al, 2007; Chia et al, 2008; Ross et al, 2009) and is a marker of the HER2-positive and luminal-B intrinsic sub-types of breast cancer (Sorlie et al, 2004). HER2 overexpression/amplification ('HER2-positivity') is associated with increased tumour aggressiveness, higher rates of recurrence, and increased mortality (Borg et al, 1990; Ross et al, 1998; Menard et al, 2001; Brown et al, 2008; Curigliano et al, 2009; Ross et al, 2009).

Surgery is the main modality of local treatment for breast cancer, and surgery and/or radiotherapy can control loco-regional disease in the majority of patients. Conventionally, adjuvant systemic therapy is given after loco-regional therapy to eradicate micrometastatic disease and reduce the chances of

distant (and local) relapse (European Society for Medical Oncology (ESMO) Clinical Recommendations, 2013).

Neoadjuvant therapy is given prior to surgery and has become a treatment option for patients with newly diagnosed breast cancer. Although originally developed for patients with large and/or inoperable tumours to enable definitive surgery to be performed, neoadjuvant therapy may also be used in patients with operable early breast cancer to try to avoid a mastectomy and enable breast-conserving surgery (BCS) to take place. Neoadjuvant therapy is also the primary modality of therapy for patients with inflammatory breast cancer, regardless of tumour size (Dawood et al, 2011). According to the US National Comprehensive Cancer Network (NCCN) Guidelines and ESMO Clinical Recommendations the treatment modalities (chemotherapy, endocrine therapy, targeted therapy) used in adjuvant treatment may also be used pre-operatively.

Neoadjuvant treatment of HER2 positive early breast cancer include trastuzumab which is indicated in combination with neoadjuvant chemotherapy followed by adjuvant trastuzumab therapy, for locally advanced (including inflammatory) disease or tumours > 2 cm in diameter (EPAR Herceptin).

About the product

Pertuzumab (Perjeta) is a recombinant, humanized, immunoglobulin (Ig)G1κ monoclonal antibody, which targets the human epidermal growth factor receptor 2 (HER2, also known as c-erbB-2), a transmembrane glycoprotein with intrinsic tyrosine kinase activity.

By binding to the subdomain 2 epitope of the extracellular domain of HER2, Pertuzumab prevents hetero-dimerization of HER2 with other members of the HER family (HER1, HER3 and HER4). As a result, ligand-activated downstream signalling is blocked by pertuzumab. Pertuzumab is also capable of activating antibody-dependent cell-mediated cytotoxicity (ADCC). When combined with trastuzumab, pertuzumab provides a more complete blockade of the HER pathway resulting in augmented anti-cancer activity in patients with HER2-positive breast cancer.

Pertuzumab was authorised on 4 March 2013 in the following indication:

Perjeta is indicated for use in combination with trastuzumab and docetaxel in adult patients with HER2-positive metastatic or locally recurrent unresectable breast cancer, who have not received previous anti-HER2 therapy or chemotherapy for their metastatic disease.

The present application is to extend the use of Perjeta for the neoadjuvant treatment of patients with HER2-positive breast cancer.

The applied indication was:

Perjeta is indicated in combination with trastuzumab and docetaxel for the neoadjuvant treatment of patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer (> 2 cm in diameter) as part of the treatment for early breast cancer.

The recommended indication is:

Perjeta is indicated for use in combination with trastuzumab and chemotherapy for the neoadjuvant treatment of adult patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer at high risk of recurrence (see section 5.1.).

The recommended initial loading dose of Perjeta is 840 mg administered as a 60 minute intravenous infusion, followed every 3 weeks thereafter by a maintenance dose of 420 mg administered over a period of 30 to 60 minutes.

When administered with Perjeta the recommended initial loading dose of trastuzumab is 8 mg/kg body weight administered as an intravenous infusion followed every 3 weeks thereafter by a maintenance dose of 6 mg/kg body weight.

When administered with Perjeta the recommended initial dose of docetaxel is 75 mg/m^2, administered thereafter on a 3 weekly schedule. The dose of docetaxel may be escalated to 100 mg/m^2 on subsequent cycles if the initial dose is well tolerated (the docetaxel dose should not be escalated when used in combination with carboplatin, trastuzumab and Perjeta).

The medicinal products should be administered sequentially and not mixed in the same infusion bag. Perjeta and trastuzumab can be given in any order. When the patient is receiving docetaxel, this should be administered after Perjeta and trastuzumab. An observation period of 30 to 60 minutes is recommended after each Perjeta infusion and before commencement of any subsequent infusion of trastuzumab or docetaxel (see SmPC section 4.4).

Perjeta should be administered for 3 to 6 cycles in combination with neoadjuvant trastuzumab and chemotherapy, as part of a treatment regimen for early breast cancer. Following surgery, patients should be treated with adjuvant trastuzumab to complete 1 year of treatment (see SmPC sections 4.2 and 5.1).

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity / environmental risk assessment

No environmental risk assessment was submitted for pertuzumab in accordance with the "Guideline on the environmental risk assessment of medicinal products for human use" (EMEA, 2006). Proteins and peptides are exempted from the need to provide an environmental risk assessment, because they are unlikely to result in significant risk to the environment. This was considered acceptable by the CHMP.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted the results of two phase II studies, NEOSPHERE (WO20697) and TRYPHAENA (BO22280) in support of the proposed indication.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Protocol No.	Study Design	Population	Efficacy Parameters	Drug, Dose, Duration	No. of Patients Sex (M; F) ITT population
NEOSPHERE (WO20697)	A Phase II randomized, open-label, four-arm study evaluating neoadjuvant treatment with Arm A - T+D Arm B - Ptz+T+D Arm C - Ptz+T Arm D - Ptz+D	Patients with locally advanced, inflammatory or early stage HER2-positive breast cancer scheduled to receive neoadjuvant therapy.	Neoadjuvant phase: pCR rate in the breast (bpCR, ypT0/is), tumor response, clinical response rate, time to response, breast conserving surgery Adjuvant phase only: DFS, PFS	**Neoadjuvant (4 cycles):** Pertuzumab: 420 mg IV q3w (840 mg loading dose) Trastuzumab: 6 mg/kg IV q3w (8mg/kg loading dose) Docetaxel: 75mg/m^2 escalating to 100mg/m^2 IV q3w **Adjuvant treatment up to one year:** Trastuzumab: 8 mg/kg IV q3w (8mg/kg loading dose) FEC: 5-Fluorouracil: 500 mg/m^2 (dose capping at 1200 mg) Epirubicin: 100 mg/m^2 Cyclophosphamide: 600 mg/m^2, (dose capping at 1200 mg) Docetaxel: 75mg/m^2 escalating to 100mg/m^2 IV q3w (Arm C only)	417 patients (0 M; 417 F): Arm A: N = 107 Arm B: N = 107 Arm C: N = 107 Arm D: N = 96
TRYPHAENA (BO22280)	A Phase II randomized, open-label, three-arm study evaluating neoadjuvant treatment with: Arm A : Ptz+T+FEC q3w x 3 cycles → Ptz+T+D q3w x 3 cycles Arm B : FEC q3w x 3 cycles → Ptz+T+D q3w x 3 cycles Arm C: Ptz+TCH q3w x 6 cycles	Patients with locally advanced, inflammatory or early stage HER2-positive breast cancer scheduled to receive neoadjuvant therapy.	Efficacy endpoints were secondary objectives of this study: Neoadjuvant phase: pCR rate in the breast (bpCR, ypT0/is), clinical response rate, time to response, breast conserving surgery Adjuvant and Follow-up phase: DFS, PFS, OS	**Neoadjuvant (6 cycles):** Pertuzumab: 420 mg IV q3w (840 mg loading dose) Trastuzumab: 6 mg/kg IV q3w (8mg/kg loading dose) Docetaxel: 75mg/m^2 escalating to 100mg/m^2 IV q3w (in Arms A and B only) FEC (IV q3w): - 5-FU: 500mg/m^2 - Epirubicin: 100mg/m^2 - Cyclophosphamide: 600mg/m^2 Carboplatin (AUC 6 , IV q3w): the Calvert formula was used to calculate the dose **Adjuvant Treatment up to 1 Year:** Trastuzumab: 8 mg/kg IV q3w (8mg/kg loading dose)	225 patients (0 M; 225 F): Arm A: N = 73 Arm B: N = 75 Arm C: N = 77

5-FU= 5-fluorouracil, D = docetaxel, DFS = Disease-free survival, FEC = 5-Fluorouracil, epirubicin, cyclophosphamide, IRF = independent review facility,
OS = overall survival, pCR = pathological complete response, Pla = placebo, Ptz = pertuzumab, PFS = progression-free survival; q3w = every three weeks, qw = every week, T= trastuzumab, TCH = docetaxel (Taxotere)+carboplatin+trastuzumab (Herceptin)

In addition to the above studies there are two additional studies ongoing:

APHINITY (BO25126/TOC4939g/BIG-4-11):

This is an ongoing, randomized, two-arm Phase III study of adjuvant trastuzumab and chemotherapy plus pertuzumab or placebo in patients with primary operable breast cancer. Recruitment into the study is complete (4805 patients) and the Independent Data Monitoring Committees (IDMC) have reported no unexpected safety signals as of December 2013. A CHMP Scientific Advice for the APHINITY trial was sought in October 2010. The primary analysis is expected to take place in 2016 and final clinical study report in May 2017.

BERENICE (WO29217):

This is a non-randomized, open label, phase II study designed to evaluate pertuzumab in combination with trastuzumab and two different neoadjuvant anthracycline-based chemotherapy regimens in patients with HER2-positive, locally advanced, inflammatory or early stage breast cancer. The study will enrol a similar patient population to that enrolled in the NEOSPHERE and TRYPHAENA studies. The primary endpoint of the study is cardiac safety of pertuzumab in combination with two commonly used neoadjuvant regimens. Secondary endpoints include overall safety and pCR rate. The study is planned to enrol approximately 400 patients (200 patients in each cohort). Safety and efficacy data from the neoadjuvant period are anticipated in May 2017.

2.3.2. Pharmacokinetics

The MAH presented PK data from the NEOSPHERE study. In this study, optional biomarker sample repository (BSR) blood samples were collected from consented patients in order to better understand/predict pertuzumab/trastuzumab efficacy, dose responses, safety, pertuzumab/trastuzumab mode of action, progression of breast cancer, and associated diseases.

Pertuzumab was administered as a loading dose of 840 mg intravenous (IV) followed by 420 mg IV q3w. Trastuzumab was administered as a loading dose of 8 mg/kg IV followed by 6 mg/kg IV q3w. Docetaxel was administered at an initial dose of 75 mg/m^2 escalating to 100 mg/m^2 q3w. During the entire pre- and post-surgical period, all patients received appropriate chemotherapy as per standard of care, as well as any surgery and/or radiotherapy as required.

Pertuzumab serum concentrations were measured in BSR blood samples obtained on days 14-21 post-dose of Cycles 2 and 4 (two samples per patient were planned). Samples were obtained from 139 patients: Arm B, n=49; Arm C, n=45; and Arm D, n=45.

Trastuzumab serum concentrations were measured in BSR blood samples obtained on Days 14-21 post-dose of Cycles 2 and 4. Samples were obtained from 135 patients: Arm A, n=41; Arm B, n=49; and Arm C, n=45.

A new PK ELISA using a monoclonal anti-idiotype antibody against trastuzumab was developed and validated to measure trastuzumab in the presence of pertuzumab to enable PK evaluation for clinical trials in which both trastuzumab and pertuzumab are administered.

PK results collected in NEOSPHERE were compared with the prediction of previously developed population PK (popPK) models for pertuzumab and trastuzumab, developed with 481 and 595 patients respectively. The popPK model for pertuzumab was based on 12 clinical trials in patients with solid tumours, ovarian cancer, prostate cancer, non-small cell lung cancer and breast cancer. Lean body weight and serum albumin concentration were identified as significant covariates for pertuzumab PK in that model.

No immunogenicity data (anti-therapeutic antibodies) were collected in NEOSPHERE.

Results

Pertuzumab

With a loading dose of 840 mg and a 420 mg maintenance dose every 3 weeks (q3w), the steady-state concentrations of pertuzumab were reached after the first maintenance dose. In previously submitted studies with the same dosage schedule pertuzumab demonstrated linear PK at a dose range of 2-25 mg/kg with respect to dose proportionality and time-independence.

NEOSPHERE patients had a slightly lower median lean body weight (LBW) (44.6 kg versus 49.2 kg) and a higher median albumin (ALBU) (4.4 g/dL versus 3.9 g/dL) compared with the previous pertuzumab popPK model population but after correcting for baseline differences in weight and ALBU the popPK model predictions matched the observed pertuzumab serum concentrations. Pertuzumab Cycle 2 observed serum trough serum concentrations had a mean of 70 f.IQ/mL, and 98% (130 of 133) of patients in Arms B, C, and D had a serum trough serum concentration >20 f.IQ/mL. For the model-predicted trough serum concentrations at Cycle 2, the mean was 60 f.IQ/mL and 97% (130 of 134) of the patients had a predicted trough serum concentration >20 f.IQ/mL.

The median CL of the NEOSPHERE patient was 0.204 L/day, which was slightly lower than the typical CL of 0.235 L/day estimated in the prior popPK model.

Trastuzumab

Patients in NEOSPHERE had a slightly lower median body weight (64 kg versus 67.5 kg) and a slightly lower median serum glutamic-pyruvic transaminase (SGPT) levels (18 IU/L versus 19 IU/L) compared with the previous trastuzumab popPK model population.

The trastuzumab PK results were similar across the three arms in NEOSPHERE. The modelled PK profiles over-predicted the observed trastuzumab serum concentrations, even after correcting for baseline covariates: measured trastuzumab trough concentration at Cycle 2 was 32.4% lower than the model-predicted value. Trastuzumab Cycle 2 observed trough serum concentrations had a mean of 34 µg/mL, and 64% (83 of 129) of patients in Arms A, B, and C had a trough serum concentration >20 µg/mL. For the individual model-predicted trough serum concentrations, the mean was 36 µg/mL, and 98% (127 of 129) of the patients had a predicted trough >20 µg/mL.

The clearance in NEOSPHERE patients was higher than the values from the popPK model, even after correcting for the difference in covariates. However trastuzumab CL values were similar between patients with or without pertuzumab (p=0.103, comparing Arms A and B) and patients with or without docetaxel (p= 0.160, comparing Arms B and C).

2.3.3. Discussion on clinical pharmacology

The analysis of pertuzumab PK in NEOSPHERE showed that patients had lower lean body weight and higher serum albumin concentrations than patients in the pertuzumab pop PK model, resulting in a

lower observed clearance in NEOSPHERE patients. After correcting for baseline differences, the pop PK model represented well the pertuzumab PK observed in NEOSPHERE patients indicating that pertuzumab PK is similar between neo-adjuvant and MBC patients. Further, pertuzumab PK did not appear to vary between study treatment arms, suggesting it was not affected by the presence of co-administered trastuzumab, docetaxel, or both.

2.3.4. Conclusions on clinical pharmacology

Overall, the PK results presented suggested that the previous popPK pertuzumab model adequately described the distribution of the NEOSPHERE pertuzumab PK serum concentrations. The observed trough concentrations appeared similar across treatment groups. Therefore, drug-drug interactions are not expected between pertuzumab and trastuzumab or between pertuzumab and docetaxel. The PK results of pertuzumab in the NEOSPHERE study are consistent with the predictions from the previous population PK model (see SmPC section 5.2).

2.4. Clinical efficacy

2.4.1. Dose response study

No formal dose-response studies were conducted for this indication, which was considered acceptable by the CHMP. The proposed dose of pertuzumab in the neoadjuvant setting is the same as the dose used in the metastatic setting.

2.4.2. Main studies

Study NEOSPHERE (WO20697)

Study NEOSPHERE is a randomised, multicenter, multinational Phase II study evaluating the combination of trastuzumab plus docetaxel versus trastuzumab plus docetaxel plus pertuzumab versus trastuzumab plus pertuzumab versus pertuzumab and docetaxel in patients with locally advanced, inflammatory or early stage HER2 positive breast cancer.

Methods

Study participants

Inclusion criteria

Disease specific inclusion criteria:

1. Female patients with locally advanced, inflammatory or early stage, unilateral and histologically confirmed invasive breast cancer.

2. Primary tumour > 2 cm in diameter.

3. HER2-positive breast cancer confirmed by a central laboratory. Tumours had to be HER2+++ by IHC or FISH/CISH + (FISH/CISH mandatory for HER2 ++ tumours).

4. Availability of formalin-fixed, paraffin-embedded tissue for central confirmation of HER2 eligibility (FFPE tumour tissue was subsequently to be used for assessing status of biomarkers).

General inclusion criteria:

1. Age ≥ 18 years.

2. Baseline left ventricular ejection fraction (LVEF) ≥ 55% (measured by echocardiography or MUGA).

3. Performance status ECOG ≤ 1.

4. At least 4 weeks since major unrelated surgery, with full recovery.

5. Availability of a negative pregnancy test for pre-menopausal women and for women less than 2 years after the onset of menopause.

6. Signed informed consent.

Exclusion criteria

Cancer-related exclusion criteria:

1. Metastatic disease (Stage IV) or bilateral breast cancer.

2. Previous anticancer therapy or radiotherapy for any malignancy.

3. Other malignancy, except for carcinoma in situ of the cervix or basal cell carcinoma.

Haematological, biochemical and organ function:

4. Inadequate bone marrow function (e.g., Absolute Neutrophil Count (ANC) < 1.5 x 10^9/L, platelet count < 100 x 10^9/L and Hb < 9 g/dL).

5. Impaired liver function: (e.g., serum [total] bilirubin > 1.25 x ULN (with the exception of Gilbert's syndrome), AST, ALT > 1.25 x ULN, albumin < 25 g/L).

6. Inadequate renal function, serum creatinine > 1.5 x ULN.

7. Uncontrolled hypertension (systolic > 150 and/or diastolic > 100), unstable angina, congestive heart failure (CHF) of any New York Heart Association (NYHA) classification, serious cardiac arrhythmia requiring treatment (exception: atrial fibrillation, paroxysmal supraventricular tachycardia), history of myocardial infarction within 6 months of enrollment, or LVEF < 55%.

8. Dyspnoea at rest or other diseases which required continuous oxygen therapy.

Other study drug-related exclusion criteria:

General Exclusion Criteria

9. Severe uncontrolled systemic disease (e.g., hypertension, clinically significant cardiovascular, pulmonary, metabolic, wound-healing, ulcer, or bone fracture).

10. Patients with insulin-dependent diabetes.

11. Pregnant and/or lactating women.

12. Patients with reproductive potential not willing to use highly effective non-hormonal method of contraception or two effective forms of non-hormonal contraception, which must continue for the duration of study treatment and for at least 6 months post discontinuation of study treatment.

13. Patients receiving any investigational treatment within 4 weeks of study start.

14. Patients with known infection with HIV, HBV or HCV.

15. Known hypersensitivity to any of the study drugs or excipients.

16. Patients assessed by the investigator to be unable or unwilling to comply with the requirements of the protocol.

Treatments

Study treatment in this study was defined as neoadjuvant (pre-operative) and adjuvant (post-operative surgery) treatment. Throughout the study, the investigational medicinal products were pertuzumab and trastuzumab; docetaxel, 5-fluorouracil, epirubicin, and cyclophosphamide were administered in accordance with their Summary of Product Characteristics and/or standard practice and are therefore not regarded as Investigational Medicinal Products.

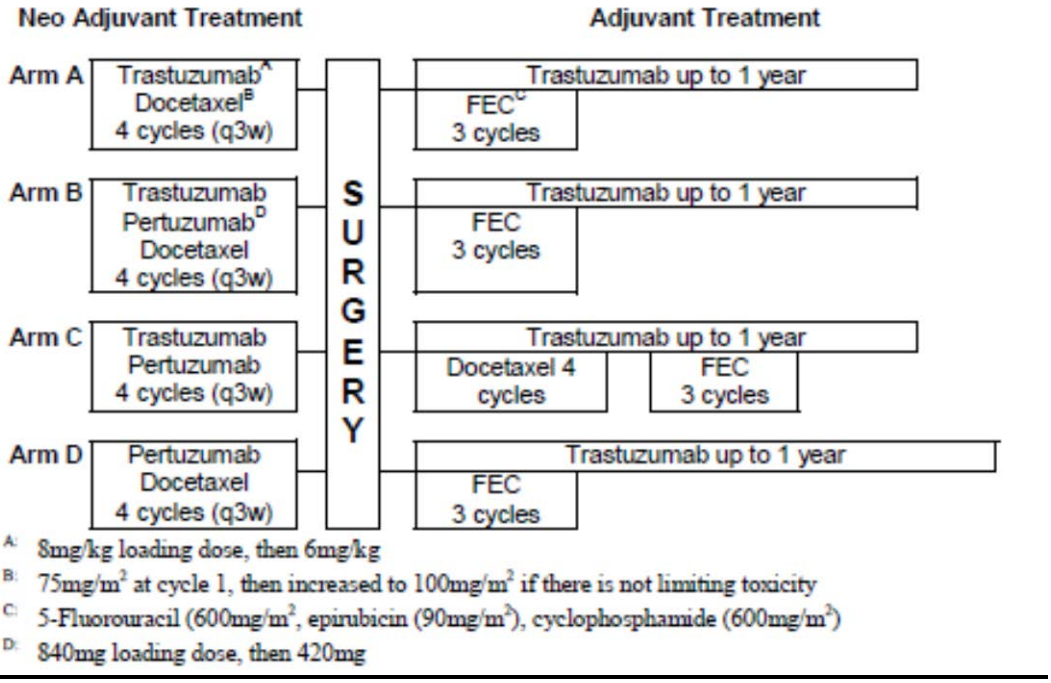


Figure 1: Overall study design

Neoadjuvant (Pre-Operative) Treatment

Study treatment was administered every 3 weeks for 4 cycles, as follows, prior to breast surgery:

• Arm A: Trastuzumab IV + docetaxel IV (T+D)

A loading dose of 8 mg/kg of trastuzumab was required on Day 1, Cycle 1, and a maintenance dose of 6 mg/kg thereafter. The starting dose for docetaxel was 75 mg/m^2 for Cycle 1 then 100 mg/m^2 for Cycles 2-4, if no dose limiting toxicity occurred.

• Arm B: Trastuzumab IV + pertuzumab IV + docetaxel IV (Ptz+T+D)

A loading dose of 8 mg/kg of trastuzumab and 840 mg of pertuzumab was required on Day 1 Cycle 1; thereafter, maintenance doses of 6 mg/kg and 420 mg, respectively, were required from Cycle 2 onward. The starting dose for docetaxel was 75 mg/m^2 for Cycle 1, then 100 mg/m^2 for Cycles 2−4, if no dose-limiting toxicity occurred.

• Arm C: Trastuzumab IV + pertuzumab IV (Ptz+T)

A loading dose of 8 mg/kg of trastuzumab and 840 mg pertuzumab was required on Day 1 Cycle 1; thereafter, a maintenance dose of 6 mg/kg and 420 mg, respectively, were required from Cycle 2 onward.

• Arm D: Pertuzumab IV + docetaxel IV (Ptz+D)

A loading dose of 840 mg of pertuzumab was required on Day 1 Cycle 1; thereafter, a maintenance dose of 420 mg was required from Cycle 2 onward. The starting dose for docetaxel was 75 mg/m^2 for Cycle 1, then 100 mg/m^2 for Cycles 2-4, if no dose-limiting toxicity occurred.

Adjuvant (Post-Operative) Treatment

• Arms A, B, and D:

Patients in Arms A, B, and D received trastuzumab 6 mg/kg IV followed by FEC (5-fluorouracil 600 mg/m^2 IV, epirubicin 90 mg/m^2 IV, then cyclophosphamide 600 mg/m^2 IV) on Day 1 and every 3 weeks thereafter for three cycles (i.e., Cycles 5 – 7), with each cycle lasting 21 days. Cycle 5 administration was not to occur until 2 weeks after surgery. Thereafter, trastuzumab 6 mg/kg IV was to be given every 3 weeks from Cycle 8 continuing until Cycle 17 for patients in Arms A and B and until Cycle 21 for patients in Arm D.

• Arm C:

Patients in Arm C received trastuzumab 6 mg/kg IV followed by docetaxel 75 mg/m^2 IV for Cycle 5. From Cycle 6, docetaxel was escalated to 100 mg/m^2 for three cycles (i.e., Cycles 6 – 8) if no dose-limiting toxicity occurred. For Cycles 9 to 11, patients received trastuzumab 6 mg/kg IV followed by FEC (5-fluorouracil 600 mg/m^2 IV, epirubicin 90 mg/m^2 IV, then cyclophosphamide 600 mg/m^2 IV) on Day 1 and every 3 weeks thereafter for three cycles (each cycle lasting 21 days). From Cycle 12 until Cycle 17, trastuzumab 6 mg/kg IV was continued.

Objectives

Primary Objectives

- To make a preliminary assessment of the efficacy of neoadjuvant treatment of trastuzumab plus docetaxel, as compared to trastuzumab, pertuzumab plus docetaxel or to trastuzumab plus pertuzumab, and to compare pertuzumab plus docetaxel with trastuzumab, pertuzumab plus docetaxel, in patients with T2-4d HER2-positive breast cancer, based on complete pathological response rate. The primary objective was evaluated when all patients received 4 cycles of neoadjuvant treatment and surgery or had withdrawn from the study whichever was earlier.

Secondary Objectives

- To evaluate the safety profiles of each treatment regimen, including pre-operative (neoadjuvant) and post-operative (adjuvant) treatment.
- To determine the time to clinical response, time-to-response, disease free survival (DFS) and progression-free survival (PFS) for each treatment arm.
- To evaluate the biomarkers that may be associated with primary and secondary efficacy endpoints in accordance with each treatment arm.
- To evaluate the rate of breast conservative surgery for all patients with T2-3 tumors for whom mastectomy was planned at diagnosis.

- To make a preliminary assessment of the efficacy of neoadjuvant treatment of pertuzumab and docetaxel.

Outcomes/endpoints

Primary endpoint: Post-surgery pathologic complete response (pCR) rate in the breast

The primary endpoint was post-surgery pCR rate in the breast, evaluated after patients had received 4 cycles of treatment and surgery or had withdrawn from the study, whichever occurred first.

Definition of pCR: pCR is defined as absence of invasive neoplastic cells in the breast at microscopic examination of the tumor remnants after surgery following primary systemic therapy.

Absence of residual *in situ* disease was not required for a pCR in these studies. This definition is abbreviated to bpCR (pathological complete response in the breast) and corresponds to the definition, ypT0/is, according to the TNM classification.

Two other more stringent definitions of pCR are in common use: tpCR (total pCR) and GBG pCR (German Breast Group pCR). Differences among these definitions are reported in the Table below.

Table 1: pCR Definitions

Terminology (abbreviation) used in this document	**pCR Definition**		
	Breast pathologic complete response (bpCR)	**Total pathologic complete response (tpCR)**	**GBG pathologic complete response (GBG pCR)**
TNM Staging System*	ypT0/is	ypT0/is ypN0	ypT0 ypN0
Description	Eradication of all invasive tumor from the breast (in situ disease might remain); nodal status not considered	Eradication of all invasive tumor from the breast (in situ disease might remain) and node negative at definitive surgery	Eradication of all invasive and non-invasive tumor from the breast (no remaining in situ disease) and node negative at definitive surgery
*TNM classification (confirmed by pathology after initial treatment): y = status post initial therapy; T = tumor; N = nodes; is = in situ; EBC = early breat cancer; GBG = German Breast Group; I-SPY = Investigation of Serial Studies to Predict Your Therapeutic Response with Imaging and Molecular Analysis; NSABP = National Surgical Adjuvant Breast and Bowel Project			

Note: The MAH justified the choice of the bpCR definition as that preferred by Michelangelo Foundation (a scientific non-profit organization dedicated to the advancement of cancer research and involved in EBC research) at the time of study design. However, in view of the uncertainty surrounding the most appropriate definition of pCR to use, and to enable cross-trial comparisons, data were prospectively collected in both NEOSPHERE and TRYPHAENA to allow assessment of pCR by all three definitions. Pathological complete response rates according to the tpCR and GBG pCR definitions are considered exploratory endpoints for both studies (see section on Comparison across trials, pCR by definition).

The pCR rate is the proportion of the intent-to-treat (ITT) population that achieve a pCR.

Assessment of tumour specimens by the pathologist was done according to institutional standards for processing and interpretation of pathologic specimens was maintained as per local practice. There was no centralised review of the pathology specimens.

Secondary endpoints:

Clinical response rate: Clinical response was defined as complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). Clinical response rate was defined as the proportion

of patients who achieved a clinical response (CR or PR) during Cycles 1-4 (pre-surgery). Clinical response was to be assessed at each cycle, between Days 15-21 or on study Day 1 of the next cycle.

The clinical response during neo-adjuvant period or the clinical response at the last assessment was to be determined based on the tumour measurements by the MAH in combination with the tumour response assessment (PD or No-PD) by the investigator. Tumour response was assessed using clinical breast examination (CBE) of the breast, axilla and supraclavicular fossa and/or mammography or other conventional methods prior to each cycle of therapy, as per local medical practice. CBE and mammography were required at baseline and after completion of Cycle 4, prior to surgery.

Baseline breast tumour assessments measured by mammogram and CBE were mandatory, but any additional assessments employing conventional methods, (ultrasound, CT scan, X-rays, MRI) were also collected. During the neoadjuvant treatment phase and after completion of all pre-operative treatment cycles, tumour response assessment could be performed using any of the conventional methods, provided that the same techniques were used for evaluating the target lesion.

Tumour assessments were made based upon the RECIST 1.0 criteria with some modifications that were required due to the study design and eCRF pages used to capture tumour assessment data.

The best tumour response was defined separately for the primary, secondary breast lesions, all breast tumours, axillary nodes, ipsilateral supraclavicular nodes and for all nodes examined as being the best tumour response (CR>PR>SD>PD) a patient achieved during the neoadjuvant period.

The overall best tumour response was derived, based on the best tumour response for all lesions (breast and nodes).

Time to clinical response: This is defined as the time to clinical response, i.e. the time from the date of first dose received to the first date of assessment of clinical response.

Breast conserving surgery (BCS) rate: This is defined as the proportion of patients with T2-T3 disease for whom a mastectomy was planned at study entry, and who subsequently underwent BCS. Patients with inflammatory breast cancer were excluded from this analysis since these patients underwent mastectomy irrespective of their response to neo-adjuvant treatment.

Disease-free survival (DFS): This is defined as the time from the first date of no disease (i.e. date of surgery) to the first documentation of progressive disease (PD) or death. Evidence of contralateral in situ disease was not to be considered PD.

Progression-free survival (PFS): This is defined as the time from the date of randomization to the first documentation of progressive disease or death from any cause. Patients without post-baseline assessments but known to be alive were censored at the time of randomization.

Evaluation of biomarkers: Tumour samples from the primary tumour (biopsy) were collected and tested in a central pathology laboratory for HER2 status and tumour tissue biomarkers for pertuzumab/trastuzumab response prediction.

For eligible patients, the following biomarkers, that may be predictive of response to pertuzumab/trastuzumab and/or prognostic for breast cancer, were assessed in tumour tissue:

– expression of HER-family receptors or related receptor-tyrosine kinases e.g., IGF1-R, EGFR, HER2, HER3, assessed by qRT-PCR and/or IHC

– HER ligands (amphiregulin and betacellulin) assessed by qRT-PCR

– Markers/components of the HER signal transduction or alternative signalling pathways (pAKT and PTEN protein expression assessed by IHC; c-myc, gene amplification assessed by FISH, mutational status of PIK3CA assessed by a PCR based assay)

Sample size

400 patients were planned to be randomized into the study. With 400 patients and an overall alpha level of 0.2 the study would have 80% power to detect an absolute percentage increase of 15% between each of the three primary comparisons.

Randomisation

Patients were randomly assigned, by a central randomization centre using dynamic allocation in the order in which they were enrolled, to Arm A, B, C or D and stratified by operable (T2-3, N0-1, M0), locally advanced (T2-3, N2 or N3, M0; T4a-c, any N, M0) and inflammatory (T4d, any N, M0) breast cancer and oestrogen and/or progesterone positivity.

Blinding (masking)

The study was open-label. Pathologists were not formally blinded as to treatment allocation.

Statistical methods

A pCR rate of 25% was expected in arm A (trastuzumab and docetaxel) and arm D (pertuzumab and docetaxel). A pCR rate of 40% in arm B (trastuzumab, pertuzumab and docetaxel) or arm C (trastuzumab and pertuzumab) was to be considered of clinical interest. The following three individual hypotheses were tested using a two-sided Cochrane Mantel-Haenszel test at an alpha level of 0.2.

Arm A versus arm B

• Null hypothesis: pCR A rate = pCR B rate

• Alternative hypothesis: pCR A rate ≠ pCR B rate

Arm A versus arm C

• Null hypothesis: pCR A rate = pCR C rate

• Alternative hypothesis: pCR A rate ≠ pCR C rate

Arm D versus arm B

• Null hypothesis: pCR D rate = pCR B rate

• Alternative hypothesis: pCR D rate ≠ pCR B rate

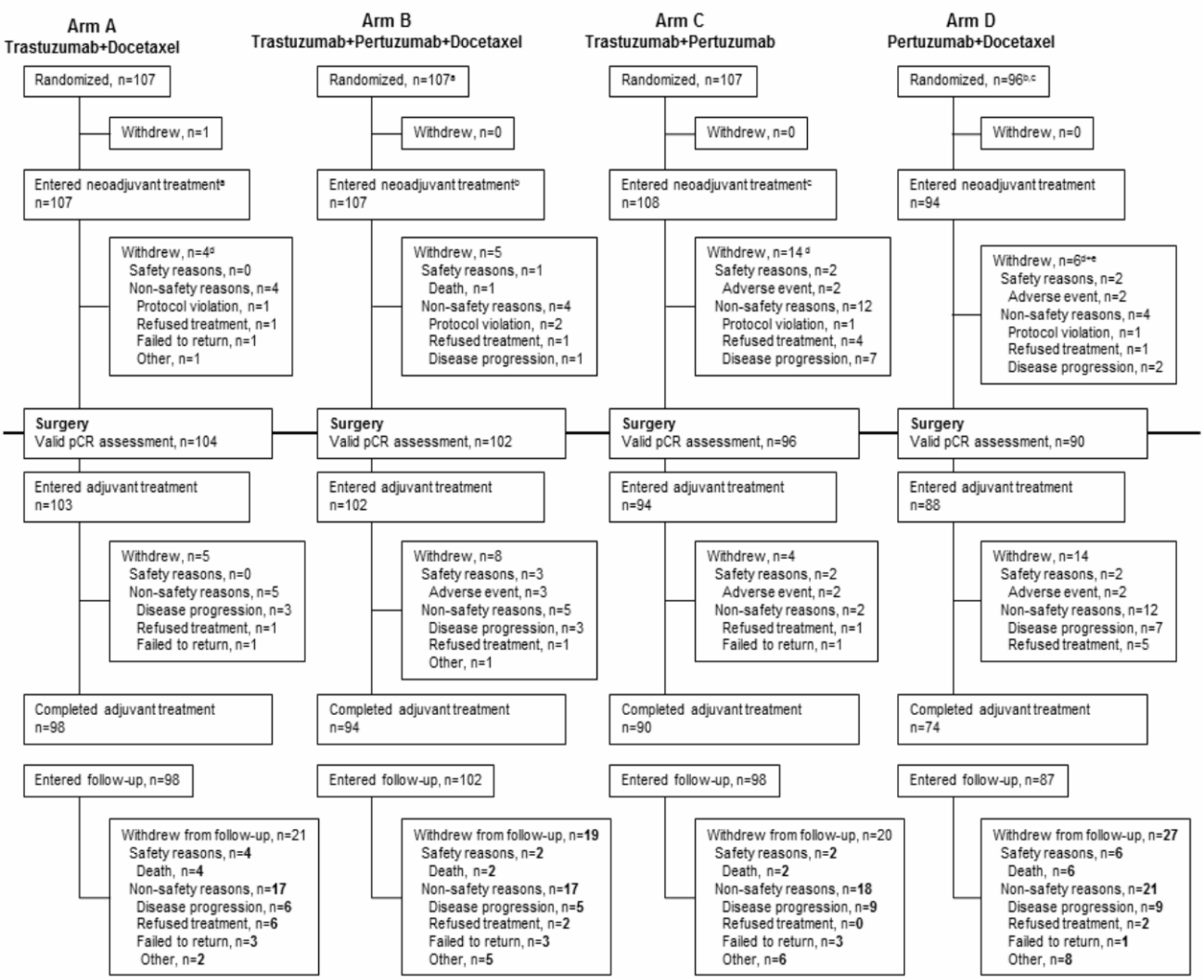
As there were three individual comparisons a Simes multiplicity adjustment was applied to the individual p-values obtained at the end of the study to maintain the overall false positive risk at 0.2.

The ITT population includes all randomized patients, regardless of whether they received any study medication. All efficacy outputs were produced for the ITT population. The per protocol (PP) population, is a subset of the ITT population. It excludes patients who were deemed to have any major protocol violations prior to the adjuvant phase of the study. The PP population includes patients who received ≥ 3 cycles (and not > 4 cycles) of their randomized study medication in the neoadjuvant setting. The PP analysis was to occur only if this population differs in total number of patients by ≥ 10% of the ITT population.

The safety population includes patients who received at least one dose of study medication and at least one safety assessment performed at baseline. Patients were assigned to treatment groups according to treatment actually received.

Results

Participant flow



Note: Withdrawal indicates withdrawal from study treatment. Patients withdrawing from treatment could still undergo primary surgery and could still be ongoing in the post-treatment follow-up period. Withdrawal at any time up to the first adjuvant trial treatment cycle was counted as withdrawal from the neoadjuvant phase.
a One patient randomized to Arm D actually received Arm A treatment, and was therefore included in the Arm A safety population.
b One Patient was randomized to Arm D but received treatment according to Arm B.
c One Patient was randomized to Arm B but received treatment according to Arm C.
d One Patient withdrew from adjuvant treatment due to an adverse event of left ventricular dysfunction, incorrectly reported as interruption of study treatment.
e One patient: updated since Primary CSR due to reporting error in neoadjuvant period.

Figure 2: Patient Disposition Flowchart for NEOSPHERE (All Patients)

Recruitment

Recruitment occurred between 17 December 2007 and 22 December 2009. All enrolled patients had completed treatment and were either in follow-up or had withdrawn from the study as of 15 February 2011. Patients were recruited across 59 centres in 16 countries (Australia, Austria, Brazil, Canada, Italy, Mexico, Peru, Poland, Republic of Korea, Russian Federation, Spain, Sweden, Switzerland, Taiwan, Thailand, United Kingdom).

Conduct of the study

Protocol Amendments

Version B (dated 4th December, 2007) introduced the following changes:

- Addition of a fourth treatment arm (arm D), in order to evaluate the efficacy of pertuzumab, in the absence of trastuzumab, in the neoadjuvant setting, with corresponding update of schedule of assessment and dosing information. There was a total of 29 patients who had been recruited on the original protocol prior to introduction of this arm.
- Increase in the number of patients participating in the study from 180 to 400, and corresponding increase in the number of centers, from 45-55 to 100.
- Amendment of efficacy endpoints, hypothesis testing and analyses to reflect addition of arm D and increased patient numbers.
- Addition of an exclusion criterion, to exclude patients with insulin-dependent diabetes from the study.
- Clarification of the offset dosing schedule.

Version C (11th December 2008) made the following change:

Correction of the tumour-node-metastasis (TNM) classes used to classify patients' disease for the stratification groups operable, locally advanced, or inflammatory cancer for this study.

Version D (27th June 2009) made the following significant changes:

• Updates to: the definition of post-menopausal women, the contraceptive requirements for women of child bearing potential in accordance with the ICH M3 guideline, and the pregnancy testing scheduling.
• Clarification of clinical response definition.

Protocol Deviations

The majority of protocol deviations reported were minor and did not exclude patients from the Per Protocol (PP) population. Across the treatment arms between 8 and 11 patients (7.5-10.3%) per arm reported at least one inclusion criteria violation, of which the majority was due to a positive or missing baseline pregnancy test result. Between 7 and 14 patients (6.5-13.1%) reported at least one exclusion criteria violation, the most common of which was missing data for, or impaired liver function. Five to 11 patients (4.7-10.3%) recorded a protocol deviation whilst on study, for various reasons.

One patient had a pulmonary lesion that was confirmed as metastases, which violated exclusion criteria. The patient was withdrawn from the study after receiving 2 cycles of treatment. Two patients had missing screening values and were reported as having a violation of primary tumour measuring less than 2 cm. However, both patients had cycle 1 tumour measurement values > 2 cm.

Baseline data

Table 2: Summary of demographic data by trial treatment (ITT Population)

Protocol(s): WO20697
Analysis: ITT (BY TREATMENT RANDOMIZED) Center: ALL CENTERS
Snapshot Date: 22FEB2010 Clinical Cut-Off Date: 22DEC2009

	Total N = 417	Trastuzumab + Docetaxel N = 107	Trastuzumab + Pertuzumab + Docetaxel N = 107	Trastuzumab + Pertuzumab N = 107	Pertuzumab + Docetaxel N = 96
Sex					
MALE	-	-	-	-	-
FEMALE	417 (100%)	107 (100%)	107 (100%)	107 (100%)	96 (100%)
n	417	107	107	107	96
Age in years					
Mean	49.8	50.9	49.6	49.7	48.9
SD	10.04	8.94	10.05	10.67	10.50
SEM	0.49	0.86	0.97	1.03	1.07
Median	50.0	50.0	50.0	49.0	49.0
Min-Max	22 - 80	32 - 74	28 - 77	22 - 80	27 - 70
n	417	107	107	107	96
Weight in kg					
Mean	67.26	68.41	67.37	68.65	64.31
SD	15.365	15.416	16.653	14.884	14.128
SEM	0.755	1.512	1.610	1.439	1.442
Median	65.00	65.50	64.00	67.00	62.30
Min-Max	28.7 - 131.0	40.5 - 119.6	40.0 - 131.0	28.7 - 106.0	44.0 - 131.0
n	414	104	107	107	96
Height in cm					
Mean	159.8	159.4	159.9	160.0	159.9
SD	6.98	7.04	6.76	7.10	7.13
SEM	0.34	0.68	0.65	0.69	0.73
Median	160.0	159.0	160.0	161.0	159.5
Min-Max	128 - 178	140 - 178	146 - 176	128 - 178	145 - 176
n	416	106	107	107	96
Race					
BLACK	6 (1.4%)	-	2 (1.9%)	1 (0.9%)	3 (3.1%)
CAUCASIAN	297 (71.2%)	80 (74.8%)	77 (72.0%)	79 (73.8%)	61 (63.5%)
ORIENTAL	95 (22.8%)	25 (23.4%)	23 (21.5%)	22 (20.6%)	25 (26.0%)
OTHER	19 (4.6%)	2 (1.9%)	5 (4.7%)	5 (4.7%)	7 (7.3%)
n	417	107	107	107	96
Female Reproductive Status					
POSTMENOPAUSAL	183 (43.9%)	48 (44.9%)	45 (42.1%)	50 (46.7%)	40 (41.7%)
SURGICALLY STERIL.	27 (6.5%)	7 (6.5%)	7 (6.5%)	4 (3.7%)	9 (9.4%)
WITH CONT. PROT.	207 (49.6%)	52 (48.6%)	55 (51.4%)	53 (49.5%)	47 (49.0%)
n	417	107	107	107	96
ECOG Status at Baseline					
0	368 (88.5%)	100 (94.3%)	96 (89.7%)	92 (86.0%)	80 (83.3%)
1	48 (11.5%)	6 (5.7%)	11 (10.3%)	15 (14.0%)	16 (16.7%)
n	416	106	107	107	96

n represents number of patients contributing to summary statistics.
Percentages are based on n (number of valid values). Percentages not calculated if n < 10.
DM11 05MAR2010:09:38:53 (2 of 2)
Source: t_dm11_i (PDRD)

Table 3: Summary of history of breast cancer and HER2 Status by trial treatment (ITT Population)

Protocol(s): WO20697
Analysis: ITT (BY TREATMENT RANDOMIZED) Center: ALL CENTERS
Snapshot Date: 22FEB2010 Clinical Cut-Off Date: 22DEC2009

	Total N = 417	Trastuzumab + Docetaxel N = 107	Trastuzumab + Pertuzumab + Docetaxel N = 107	Trastuzumab + Pertuzumab N = 107	Pertuzumab + Docetaxel N = 96
Hormone Receptor Positivity					
Estrogen and Progesterone Negative	219 (52.6%)	57 (53.3%)	57 (53.3%)	55 (51.9%)	50 (52.1%)
Estrogen and/or Progesterone Positive	197 (47.4%)	50 (46.7%)	50 (46.7%)	51 (48.1%)	46 (47.9%)
n	416	107	107	106	96
Breast Cancer Type					
INFLAMMATORY	29 (7.0%)	7 (6.5%)	10 (9.3%)	7 (6.5%)	5 (5.2%)
LOCALLY ADVANCED	134 (32.1%)	36 (33.6%)	32 (29.9%)	35 (32.7%)	31 (32.3%)
OPERABLE	254 (60.9%)	64 (59.8%)	65 (60.7%)	65 (60.7%)	60 (62.5%)
n	417	107	107	107	96
HER2 Status IHC					
2+	31 (7.5%)	8 (7.5%)	6 (5.7%)	13 (12.4%)	4 (4.3%)
3+	380 (92.5%)	99 (92.5%)	100 (94.3%)	92 (87.6%)	89 (95.7%)
n	411	107	106	105	93
HER2 Status FISH					
NK	3 (3.2%)	1 (4.8%)	1 (5.0%)	1 (3.6%)	-
POSITIVE	90 (96.8%)	20 (95.2%)	19 (95.0%)	27 (96.4%)	24 (100%)
n	93	21	20	28	24
HER2 Status IHC/FISH Combined					
-/FISH POSITIVE	6 (1.4%)	-	1 (0.9%)	2 (1.9%)	3 (3.1%)
IHC 2+/FISH POSITIVE	31 (7.4%)	8 (7.5%)	6 (5.6%)	13 (12.1%)	4 (4.2%)
IHC 3+/-	324 (77.7%)	86 (80.4%)	87 (81.3%)	79 (73.8%)	72 (75.0%)
IHC 3+/FISH NK	3 (0.7%)	1 (0.9%)	1 (0.9%)	1 (0.9%)	-
IHC 3+/FISH POSITIVE	53 (12.7%)	12 (11.2%)	12 (11.2%)	12 (11.2%)	17 (17.7%)
n	417	107	107	107	96

Percentages are based on n (number of valid values). Percentages not calculated if n < 10.
n represents number of patients contributing to summary statistics.
DM11 05MAR2010:09:44:08 (2 of 2)
Source: t_dm11_db_01_i (PDRD)

Numbers analysed

Table 4: Patient disposition for NEOSPHERE (All patients)

t_ptdisp Patient Disposition (All Patients (By Treatment Randomized))
PRotocol: WO20697
Analysis: Safety (By Treatment Received)
Snapshot Date: 20OCT2014 Clinical Cut-Off Date: 20OCT2014

	Trastuzumab+ Docetaxel	Trastuzumab+ Pertuzumab+ Docetaxel	Trastuzumab+ Pertuzumab	Pertuzumab + Docetaxel	Total
Patients Randomized	107	107	107	96	417
Received neoadjuvant treatment(a)	107	107	108	94	416
Withdrew from neoadjuvant treatment	4	5	14	6	29
Withdrew from study during neoadjuvant period	1	3	7	1	12
Completed neoadjuvant period	103	102	94	88	387
Underwent surgery	104	102	96	90	392
Withdrew post surgery, prior to adjuvant treatment	0	0	2	0	2
Entered adjuvant treatment phase(b)	103	102	94	88	387
Withdrew from adjuvant treatment	5	8	4	14	31
Withdrew from study during adjuvant treatment phase	8	2	1	6	17
Completed adjuvant treatment(c)	98	94	90	74	356
Total study withdrawals during treatment phase	9	5	8	7	29
Entered post-treatment FU period	98	102	98	87	385
Withdrew from post-treatment FU period	21	19	20	27	87
Patients who completed FU	77	83	78	60	298

(FU = Follow Up)
(a)Three patients did not receive the correct treatment to which they were randomized:
randomized to Arm B but received Arm C treatment
randomized to Arm D but received Arm B treatment
randomized to Arm D but received Arm A treatment
In addition 1 patient in Arm A did not receive any treatment
(b)Three patients underwent surgery and went straight to FU:
(c)Includes Patient (Arm B) who received 16 cycles of treatment. This patient withdrew from adjuvant treatment because of an AE of left ventricular dysfunction (LVD) incorrectly reported as completion of study treatment.

Outcomes and estimation

Primary endpoint: pCR

Pathological response rates (bpCR) by treatment arm are presented in the Table below.

Table 5: Summary of pathological complete response rate including treatment comparisons (ITT population)

Protocol: WO20697
Analysis: ITT (By Treatment Randomized)
Snapshot Date: 22FEB2010 Clinical Cut-Off Date: 22DEC2009

	Trastuzumab + Docetaxel (N=107)	Trastuzumab + Pertuzumab + Docetaxel (N=107)	Trastuzumab + Pertuzumab (N=107)	Pertuzumab + Docetaxel (N=96)
Responders[1]	31 (29.0 %)	49 (45.8 %)	18 (16.8 %)	23 (24.0 %)
Non-Responders	76 (71.0 %)	58 (54.2 %)	89 (83.2 %)	73 (76.0 %)
95% CI for Response Rates[2]	[20.6; 38.5]	[36.1; 55.7]	[10.3; 25.3]	[15.8; 33.7]
Difference in Response Rates[3]		16.82	-12.15	-21.84
95% CI for Difference in Response Rates[4]		[3.5; 30.1]	[-23.8; -0.5]	[-35.1; -8.5]
p-value from CMH [5]		0.0094	0.0198	0.0010
p-value (Simes Corr. for CMH Test) [6]		0.0141	0.0198	0.0030

[1] Responders are the patients who achieved pCR and non responders are the patients who did not achieve pCR or assessment is invalid/missing.
[2] 95% CI for one sample binomial using Pearson-Clopper method.
[3] Treatment Arm B and C are compared to Arm A while Arm D is compared to Arm B
[4] Approximate 95% CI for difference of two rates using Hauck-Anderson method.
[5] Cochran-Mantel-Haenszel test stratified by breast cancer type (operable, locally advanced, or inflammatory) and estrogen and or progesterone positivity (either positive versus both negative).
[6] p-value from Cochran-Mantel-Haenszel test, with Simes multiplicity adjustment

pCR data by subgroups are presented under “Comparison performed across trials”.

Secondary endpoints

Clinical Response Rate

Clinical response analyses are presented by assessment modality. The majority of patients were assessed by mammography/X-ray or CBE. Since CBE was assessed at each neoadjuvant cycle, while mammogram/X-ray was only required to be assessed at baseline and cycle 4 as per protocol, CBE was deemed the most sensitive method of assessing tumour progression.

CR rate was highest in arm B (31%) and lowest in arm C (17%) in patients where CBE was used to assess the primary lesion. Correspondingly SD was lowest in arm B and highest in arm C. Disease progression was low in all arms.

Table 6: Summary of best tumour response during neoadjuvant treatment

Protocol: WO20697
Analysis: ITT (By Treatment Randomized)
Snapshot Date: 22FEB2010 Clinical Cut-Off Date: 22DEC2009

	Trastuzumab + Docetaxel (N=107)	Trastuzumab + Pertuzumab + Docetaxel (N=107)	Trastuzumab + Pertuzumab (N=107)	Pertuzumab + Docetaxel (N=96)
Method of Assessment: X-ray/Mammography				
Primary breast tumor				
n	71	58	61	47
Complete response	13 (18.3%)	11 (19.0%)	8 (13.1%)	9 (19.1%)
Partial response	35 (49.3%)	27 (46.6%)	22 (36.1%)	22 (46.8%)
Stable disease	22 (31.0%)	19 (32.8%)	27 (44.3%)	16 (34.0%)
Disease progression	1 (1.4%)	1 (1.7%)	4 (6.6%)	0 (0.0%)
Overall response*				
n	71	53	55	43
Complete response	13 (18.3%)	10 (18.9%)	7 (12.7%)	8 (18.6%)
Partial response	35 (49.3%)	26 (49.1%)	19 (34.5%)	20 (46.5%)
Stable disease	22 (31.0%)	16 (30.2%)	25 (45.5%)	15 (34.9%)
Disease progression	1 (1.4%)	1 (1.9%)	4 (7.3%)	0 (0.0%)
Method of Assessment: Clinical Examination				
Primary breast tumor				
n	99	101	102	91
Complete response	23 (23.2%)	31 (30.7%)	17 (16.7%)	19 (20.9%)
Partial response	56 (56.6%)	58 (57.4%)	52 (51.0%)	46 (50.5%)
Stable disease	20 (20.2%)	12 (11.9%)	31 (30.4%)	26 (28.6%)
Disease progression	0 (0.0%)	0 (0.0%)	2 (2.0%)	0 (0.0%)
Overall response*				
n	97	100	98	88
Complete response	21 (21.6%)	25 (25.0%)	11 (11.2%)	14 (15.9%)
Partial response	58 (59.8%)	63 (63.0%)	54 (55.1%)	51 (58.0%)
Stable disease	17 (17.5%)	12 (12.0%)	31 (31.6%)	23 (26.1%)
Disease progression	1 (1.0%)	0 (0.0%)	2 (2.0%)	0 (0.0%)

Percentages are based on n which is based on modality
*Overall response is derived based on the sum total of breast tumors and all nodes examined.

The majority of patients achieved an unconfirmed clinical response (i.e., CR or PR) in the primary lesion, as assessed by CBE (Table 6). The highest rate was reported in arm B (88.1%), followed by arm A (79.8%) then arm D (71.4%), and the lowest was in arm C (67.6%).

Table 7: Summary of clinical response during neoadjuvant treatment by method of assessment

Protocol: WO20697
Analysis: ITT (By Treatment Randomized)
Snapshot Date: 22FEB2010 Clinical Cut-Off Date: 22DEC2009

	Trastuzumab + Docetaxel (N=107)	Trastuzumab + Pertuzumab + Docetaxel (N=107)	Trastuzumab + Pertuzumab (N=107)	Pertuzumab + Docetaxel (N=96)
Method of Assessment: X-ray/Mammography				
Primary breast tumor				
Responders [1]	48 (67.6%)	38 (65.5%)	30 (49.2%)	31 (66.0%)
Non-responders	23 (32.4%)	20 (34.5%)	31 (50.8%)	16 (34.0%)
95% CI for Response Rates[2]	[55.5; 78.2]	[51.9; 77.5]	[36.1; 62.3]	[50.7; 79.1]
n	71	58	61	47
Overall response*				
Responders [1]	48 (67.6%)	36 (67.9%)	26 (47.3%)	28 (65.1%)
Non-responders	23 (32.4%)	17 (32.1%)	29 (52.7%)	15 (34.9%)
95% CI for Response Rates[2]	[55.5; 78.2]	[53.7; 80.1]	[33.7; 61.2]	[49.1; 79.0]
n	71	53	55	43
Method of Assessment: Clinical Examination				
Primary breast tumor				
Responders [1]	79 (79.8%)	89 (88.1%)	69 (67.6%)	65 (71.4%)
Non-responders	20 (20.2%)	12 (11.9%)	33 (32.4%)	26 (28.6%)
95% CI for Response Rates[2]	[70.5; 87.2]	[80.2; 93.7]	[57.7; 76.6]	[61.0; 80.4]
n	99	101	102	91
Overall response*				
Responders [1]	79 (81.4%)	88 (88.0%)	65 (66.3%)	65 (73.9%)
Non-responders	18 (18.6%)	12 (12.0%)	33 (33.7%)	23 (26.1%)
95% CI for Response Rates[2]	[72.3; 88.6]	[80.0; 93.6]	[56.1; 75.6]	[63.4; 82.7]
n	97	100	98	88

Percentages are based on n which is based on modality
[1] Responders are patients who have achieved CR or PR during the Neoadjuvant treatment, 'Unknown' is included in the non-responde category.
[2] 95% CI for one sample binomial using Pearson-Clopper method
*Overall response is derived based on the sum total of breast tumors and all nodes examined.

Time to Clinical Response (PR/CR)

Table 8: Summary of time to first clinical response (weeks) based on primary breast lesion during neoadjuvant treatment

Protocol: WO20697
Analysis: ITT (By Treatment Randomized)
Snapshot Date: 22FEB2010 Clinical Cut-Off Date: 22DEC2009

	Trastuzumab + Docetaxel (N=107)	Trastuzumab + Pertuzumab + Docetaxel (N=107)	Trastuzumab + Pertuzumab (N=107)	Pertuzumab + Docetaxel (N=96)
Method of Assessment=CLINICAL EXAMINATION				
Patients included in analysis	99	101	102	91
Patients with response	79 (79.8 %)	89 (88.1 %)	69 (67.6 %)	65 (71.4 %)
Patients without response*	20 (20.2 %)	12 (11.9 %)	33 (32.4 %)	26 (28.6 %)
Time to response [weeks]				
Median	6.3	6.3	6.9	7.3
80% CI for Median[1]	[6;7]	[4;7]	[6;9]	[6;9]
25% and 75%-ile[1]	3;10	3;8	6;10	4;10
Range[2]	3 to 13	3 to 13	3 to 13	3 to 13

*censored
[1] Kaplan-Meier estimates
[2] including censored observations

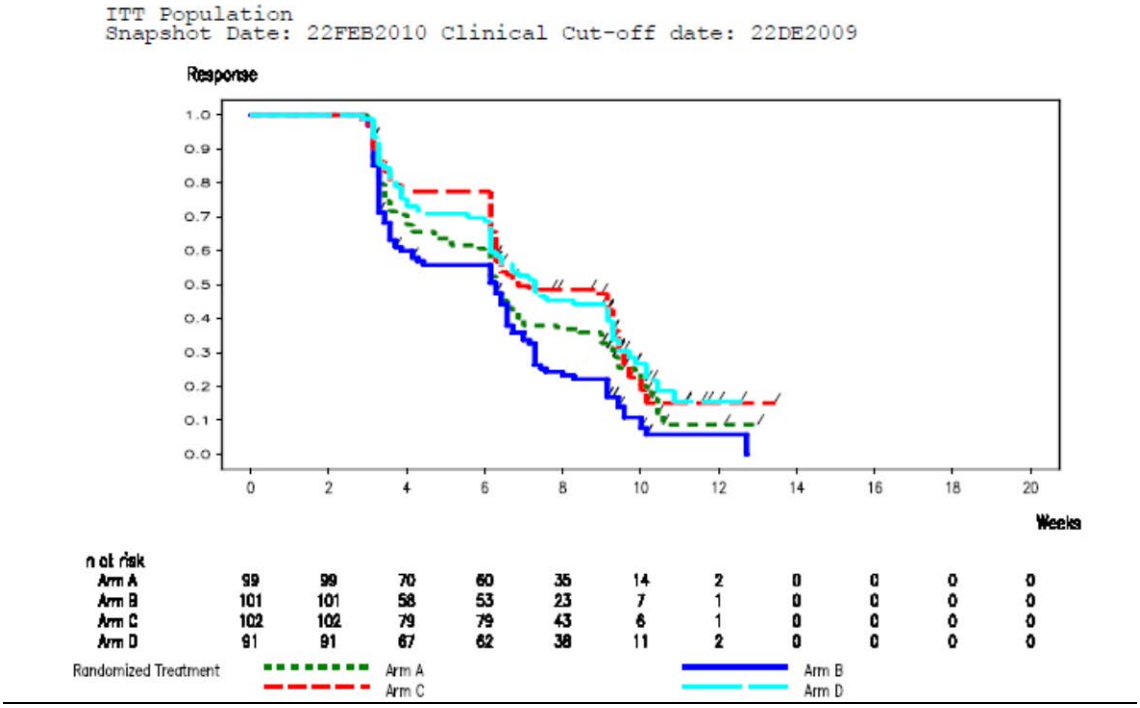


Figure 3: Kaplan-Meier plot of time to first clinical response, based on primary breast lesion (ITT population), assessed by CBE (NEOPSHERE)

Breast Conserving Surgery

Just over half the patients on study were originally planned to undergo a mastectomy. The majority of these went on to have mastectomy and/or axilliary surgical resection; however between 18-32% across the treatment arms were able to have BCS (defined as quadrantectomy or lumpectomy). The proportion of patients achieving BCS was lowest in arm C and highest in arm D.

Table 9: Summary of patients achieving breast conserving surgery (BCS) for whom mastectomy was planned

(ITT Patients with T2-3 Tumors)
Protocol: WO20697
Analysis: ITT (By Treatment Randomized)
Snapshot Date: 22FEB2010 Clinical Cut-Off Date: 22DEC2009

	Trastuzumab + Docetaxel (N=62)	Trastuzumab + Pertuzumab + Docetaxel (N=56)	Trastuzumab + Pertuzumab (N=61)	Pertuzumab + Docetaxel (N=60)
BCS Achieved [1]	14 (22.6 %)	13 (23.2 %)	11 (18.0 %)	19 (31.7 %)
BCS Not Achieved [2]	48 (77.4 %)	43 (76.8 %)	50 (82.0 %)	41 (68.3 %)
95% CI for BCS Achieved*	[12.9; 35.0]	[13.0; 36.4]	[9.4; 30.0]	[20.3; 45.0]
[1] Quadrantectomy	10 (16.1 %)	11 (19.6 %)	8 (13.1 %)	12 (20.0 %)
[1] Lumpectomy	6 (9.7 %)	3 (5.4 %)	7 (11.5 %)	12 (20.0 %)
[2] Mastectomy	47 (75.8 %)	41 (73.2 %)	42 (68.9 %)	36 (60.0 %)
[2] Missing/No Surgery	1 (1.6 %)	2 (3.6 %)	8 (13.1 %)	5 (8.3 %)
[3] Sentinel Node Biopsy	8 (12.9 %)	7 (12.5 %)	8 (13.1 %)	15 (25.0 %)
[3] Axillary Surgical Resection	51 (82.3 %)	39 (69.6 %)	47 (77.0 %)	40 (66.7 %)
[3] Other	4 (6.5 %)	1 (1.8 %)	1 (1.6 %)	2 (3.3 %)

*95% CI for one sample binomial using Pearson-Clopper method
[1] includes Quadrantectomy and lumpectomy
[2] includes mastectomy and missing/ no surgery done.
[3] includes surgeries other than mastectomy and breast conserving surgeries
If patients undergo both mastectomy and breast conserving surgery then only counted under mastectomy.
Patients for whom planned surgery was not mastectomy or is missing are excluded from this table.
Percentages are based on mastectomy planned (n)
patients may undergo more than one type of surgery, hence number of patients may not add up to number of patients in the treatment group.

DFS and PFS

A planned analysis of efficacy outcomes at 5 years was completed for the NEOSPHERE study. These data are summarized below.

Table 10: Progression-free, Event-free and Disease-free Survival in NEOSPHERE (Data cut-off: 20 October 2014)[a]

	Hazard Ratio	95% Confidence Interval
PFS[b] (Arm B vs Arm A)	0.69	[0.34 , 1.4]
DFS (Arm B vs Arm A)	0.60	[0.28, 1.27]
DFS (pCR vs non-pCR, regardless of treatment arm)	0.68	[0.36, 1.26]

[a] Final CSR
[b] PFS definition in this study is the same as that commonly used for event-free survival (EFS).

Evaluation of Biomarkers

Baseline Biomarker Levels

The levels of all biomarkers were assessed at baseline, for the overall study population as well as per study arm. All biomarker baseline levels were well balanced per arm, as judged by the median level, with no notable imbalances between any of the four study arms. The number of samples analysed varied by biomarker, either for technical reasons or due to tumour tissue availability being a limiting factor (65.9% - 99.8% of patients had samples analysed across the various biomarkers). However, in general, the number of samples analysed per biomarker was well balanced across the arms and overall a high rate of sample coverage was reached for the biomarker analyses.

PIK3CA mutation status was assessed in 65.5% of the study patients. Within the overall PIK3CA biomarker population, 32% of samples were identified as carrying a PIK3CA mutation. This was also balanced across the treatment arms. For the betacellulin and amphiregulin PCR assays, whilst mRNA levels were above the specified limit of detection, the quantities detected were very small in the majority of patients. The median levels of betacellulin and amphiregulin mRNA across the treatment arms were very low, and were less than the limits of variability for these assays.

Samples from 399 patients were tested for Fc gamma receptor polymorphisms. Incidences of the phenotypes of interest were broadly balanced across the treatment arms; however numbers of patients with certain phenotypes were too low to allow further meaningful analyses.

A treatment interaction test using logistic regression was carried out to explore whether there was a relationship between biomarker levels and pCR rate. Using this test, a significant association with the treatment benefit seen in arm B compared to arm A was observed only for HER2 membrane protein levels, as assessed by IHC (odds ratio = 3.91; p = 0.0236). 17 significance tests were performed at the alpha=0.2 level, with no adjustment for multiplicity.

Ancillary analyses

For the primary endpoint, three pre-specified hypotheses were tested, and a Simes multiplicity adjustment was applied to these comparisons (of arm A versus arm B, arm A versus arm C and arm D versus arm B) accordingly. Since the pCR rate in arm D indicated that pertuzumab given as a single antibody with docetaxel has noteworthy activity, an additional post-hoc, exploratory analysis was carried out, to test the difference in pCR rates between arms A and D. This analysis showed no statistically significant difference between the arms (p=0.3263). This comparison was not pre-specified and hence was not powered to allow any firm conclusions.

Table 11: Summary of pathological completed response rate – exploratory treatment comparison Arm A vs D (ITT population)

t_rrpcr02_i Summary of Pathological Complete Response Rate - Exploratory Treatment Comparison Arm A vs. D (ITT Population)
Protocol: WO20697
Analysis: ITT (By Treatment Randomized)
Snapshot Date: 22FEB2010 Clinical Cut-Off Date: 22DEC2009

	Trastuzumab + Docetaxel (N=107)	Trastuzumab + Pertuzumab + Docetaxel (N=107)	Trastuzumab + Pertuzumab (N=107)	Pertuzumab + Docetaxel (N=96)
Responders[1]	31 (29.0 %)	49 (45.8 %)	18 (16.8 %)	23 (24.0 %)
Non-Responders	76 (71.0 %)	58 (54.2 %)	89 (83.2 %)	73 (76.0 %)
95% CI for Response Rates[2]	[20.6; 38.5]	[36.1; 55.7]	[10.3; 25.3]	[15.8; 33.7]
Difference in Response Rates[3]		16.82	-12.15	-5.01
95% CI for Difference in Response Rates[4]		[3.5; 30.1]	[-23.8; -0.5]	[-17.7; 7.7]
p-value from CMH [5]		0.0094	0.0198	0.3263
p-value (Simes Corr. for CMH Test) [6]		0.0281	0.0296	0.3263

[1] Responders are the patients who achieved pCR and non responders are the patients who did not achieve pCR or assessment is invalid missing.
[2] 95% CI for one sample binomial using Pearson-Clopper method.
[3] Treatment Arms B (T+P+D), C (T+P)and D (P+D) are compared to Arm A (T+D). A vs D comparison is not pre-specified and not powered. Use only for exploratory purposes
[4] Approximate 95% CI for difference of two rates using Hauck-Anderson method.
[5] Cochran-Mantel-Haenszel test stratified by breast cancer type (operable, locally advanced, or inflammatory) and estrogen and or progesterone positivity (either positive versus both negative).
[6] p-value from Cochran-Mantel-Haenszel test, with Simes multiplicity adjustment

Study TRYPHAENA (BO22280)

This phase II, open-label, randomized, multinational, multi-center trial was designed to evaluate the tolerability and activity, particularly with respect to cardiac function, associated with trastuzumab and pertuzumab when used in addition to anthracycline based or carboplatin-based chemotherapy regimens as neoadjuvant therapy, in patients with HER2-positive breast cancer which was early stage, and > 2 cm in diameter, or locally advanced or inflammatory.

Methods

Study Participants

Inclusion Criteria

1. Female patients with locally advanced, inflammatory or early stage, unilateral and histologically confirmed invasive breast cancer. The initial breast cancer assessment should be performed by a physician with experience in surgery for breast cancer. Patients with inflammatory breast cancer must be able to have a core needle biopsy.

2. Primary tumour > 2cm in diameter.

3. HER2-positive breast cancer confirmed by a central laboratory. Tumours must be HER2 3+ by IHC or FISH/CISH + (FISH/CISH positivity mandatory for HER2 2+ tumours).

4. Availability of FFPE tissue (Buffered Formalin method of fixation will be accepted) for central confirmation of HER2 eligibility (FFPE tumour tissue will subsequently be used for assessing status of biomarkers).

5. Female patients, age ≥ 18 years.

6. Baseline LVEF ≥ 55% (measured by echocardiography or MUGA).

7. Performance status ECOG ≤ 1.

8. At least 4 weeks since major unrelated surgery, with full recovery.

9. A negative pregnancy test must be available for pre-menopausal women and for women less than 12 months after the onset of menopause.

10. For women of childbearing potential, agreement to use a “highly-effective”, non-hormonal form of contraception or two “effective” forms of non-hormonal contraception by the patient and/or partner. Contraception must continue for the duration of study treatment and for at least 6 months after the last dose of study treatment.

11. Signed informed consent.

Exclusion Criteria

1. Metastatic disease (Stage IV) or bilateral breast cancer.

2. Previous anticancer therapy or radiotherapy for any malignancy.

3. Other malignancy, except for carcinoma *in situ* of the cervix, basal cell carcinoma or squamous cell carcinoma of the skin.

4. Inadequate bone marrow function (e.g. Absolute Neutrophil Count (ANC) < 1.5 x 10^9/L, Platelet count < 100 x 10^9/L and Hb < 9 g/dL).

5. Impaired liver function: (e.g. serum [total] bilirubin > 1.25 x ULN (with the exception of Gilbert’s syndrome), AST, ALT > 1.25 x ULN, albumin < 25 g/L.

6. Inadequate renal function, serum creatinine > 1.5 x ULN.

7. Uncontrolled hypertension (systolic > 150 and/or diastolic > 100), unstable angina, CHF of any NYHA classification, serious cardiac arrhythmia requiring treatment (exceptions: atrial fibrillation, paroxysmal supraventricular tachycardia), history of myocardial infarction within 6 months of enrollment, or LVEF < 55%.

8. Dyspnoea at rest or other diseases which require continuous oxygen therapy.

9. Severe uncontrolled systemic disease (e.g. hypertension, clinically significant cardiovascular, pulmonary, metabolic, wound-healing, ulcer, or bone fracture).

10. Patients with insulin-dependent diabetes.

11. Pregnant and/or lactating women.

12. Patients with reproductive potential not willing to use a ‘highly effective’ method of contraception or two ‘effective’ methods of contraception as described in General Inclusion Criterion number 10.

13. Received any investigational treatment within 4 weeks of study start.

14. Patients with known infection with HIV, HBV, HCV.

15. Current chronic daily treatment with corticosteroids (dose of >10 mg methylprednisolone, or equivalent [excluding inhaled steroids])

16. Known hypersensitivity to any of the study drugs or excipients.

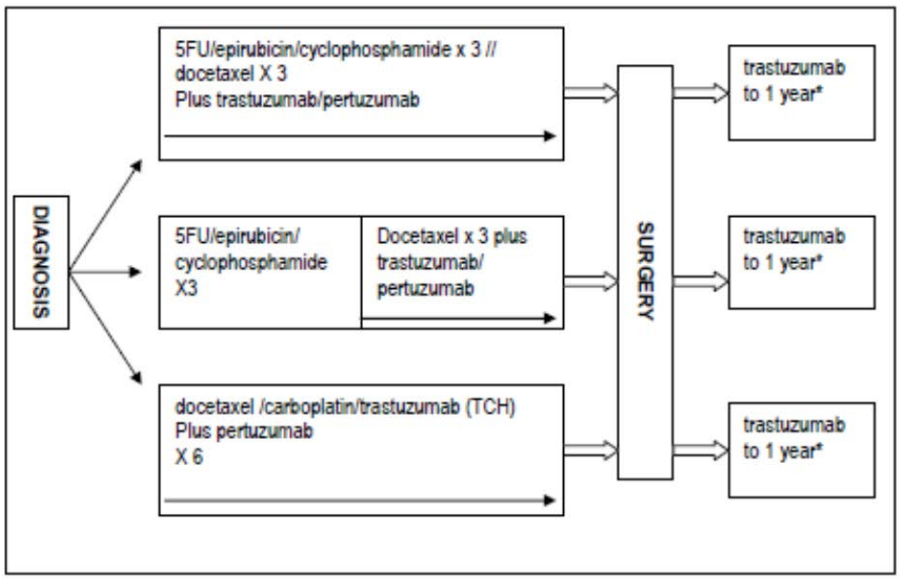
17. Patients assessed by the Investigator to be unable or unwilling to comply with the requirements of the protocol.

Treatments

Arm A: 5-Fluorouracil, epirubicin with cyclophosphamide (FEC), trastuzumab and pertuzumab every three weeks for three cycles, followed by docetaxel, trastuzumab and pertuzumab every three weeks, for three cycles. (Ptz+T+FEC/Ptz+T+D)

Arm B: FEC every three weeks for three cycles, followed by docetaxel, trastuzumab and pertuzumab every three weeks, for three cycles. (FEC/Ptz+T+D)

Arm C: Trastuzumab, carboplatin, docetaxel (TCH) and pertuzumab every three weeks, for six cycles. (Ptz+TCH)



* Additional radiotherapy, hormonal therapy and chemotherapy post-surgery and during adjuvant trastuzumab treatment is allowed if considered necessary by the investigator. Post-surgery chemotherapy was to be recommended as follows: the combination of cyclophosphamide, methotrexate and fluorouracil for patients who received anthracycline-based neoadjuvant treatment (i.e., Arms A and B), and FEC for patients who received carboplatin-based neoadjuvant treatment (i.e., Arm C).

Figure 4: Overview of the dosing schedule

Neoadjuvant

Study treatment is defined as neoadjuvant (pre-surgery) and adjuvant (post-operative surgery) treatment. The investigational medicinal products (IMPs) were pertuzumab and trastuzumab. FEC, carboplatin and docetaxel were administered in accordance with their local prescribing information and were not regarded as IMPs.

Trastuzumab was administered on Day 1 of Cycle 1 for patients in Arms A and C and Day 1 of Cycle 4 for patients in Arm B.

Pertuzumab was administered on Day 1 of Cycle 1 for Arm A and C patients and Day 1 of Cycle 4 for Arm B patients.

Docetaxel was administered at 75 mg/m^2 as an IV infusion over 60 (±10) minutes, after the pertuzumab infusion observation period. From Day 22 onwards (three weeks after the first dose), docetaxel was escalated in the subsequent cycle(s) to 100 mg/m^2 (except for patients in the pertuzumab +TCH arm [Arm C] where there was no escalation of the docetaxel dose) if no limiting toxicity was observed.

Neoadjuvant FEC was administered as an IV bolus or as an infusion (in accordance with local policy) on Day 1 of treatment in Arms A and B. FEC was given every three weeks for three cycles, as follows:

• 5-Fluorouracil was given as a dose of at 500 mg/m^2, with dose capping at 1200 mg

• Epirubicin was given as a dose of 100 mg/m^2

• Cyclophosphamide was administered at 600 mg/m^2, with dose capping at 1200 mg.

Carboplatin was given every three weeks for six cycles to patients in Arm C. The Calvert formula was used to calculate the dose (given in mg, not mg/m^2) of carboplatin: Dose (mg) = target AUC (mg/mL x min) x [GFR mL/min + 25]. Dose (mg) = 6 x [GFR mL/min + 25].

Adjuvant

Adjuvant trastuzumab was given at a dose of 6 mg/kg IV, every three weeks (q3w) from Cycle 7 onwards (which had to occur at least 2 weeks after surgery). If the interval between Cycle 6 Day 1 and Cycle 7 Day 1 was more than four weeks a reloading dose of 8 mg/kg was required for Cycle 7. Trastuzumab was to be continued for a maximum of one year in total (i.e., until Cycle 17 for Arms A and C patients and until Cycle 20 for Arm B patients).

Additional radiotherapy, hormonal therapy and chemotherapy post-surgery and during adjuvant trastuzumab treatment was to be allowed, if considered necessary by the investigator. For those patients who received anthracycline-based neoadjuvant therapy and who are deemed by the investigator to require further chemotherapy post-surgery, the combination of cyclophosphamide, methotrexate and fluorouracil (CMF) was to be suggested. For those patients who have received carboplatin-based neoadjuvant therapy and who are deemed by the Investigator to require further chemotherapy postsurgery, the regimen fluorouracil, epirubicin and cyclophosphamide (FEC) was to be suggested.

Rationale for dosage selection

Based on pharmacokinetic and clinical data, an IV dosing interval of three weeks was determined for pertuzumab (half-life of approximately 17 days). A loading dose of 840 mg (followed by 420 mg q3w), was capable of attaining steady-state trough and peak concentrations by the second cycle. The half-life of trastuzumab is approximately 28.5 days, which supports a dosing of every three weeks.

The intravenous chemotherapy regimens used for docetaxel, FEC and carboplatin are based on published data and routine clinical usage. Intravenous docetaxel was used at the starting dose of 75 mg/m^2 and was escalated up to 100 mg/m^2 according to individual tolerability. Higher doses of epirubicin were shown to be superior to lower doses of epirubicin (60 mg/m^2) in the treatment of breast cancer, and so the dose of epirubicin used in this study was 100 mg/m^2. The use of 5-fluorouracil (500 mg/m^2 IV) in combination with an anthracycline (epirubicin in this protocol) and cyclophosphamide was considered a standard regimen.

Objectives

The primary objective was to make a preliminary assessment of the tolerability of neoadjuvant treatment with one of the studied treatment regimens. The primary objective was evaluated when all patients had received six cycles of neoadjuvant treatment, had their surgery and all necessary samples taken, or withdrew from the study whichever was earlier.

The secondary objectives were:

• To make a preliminary assessment of the activity associated with each regimen as indicated by the rate of pathological complete response (pCR; defined as the absence of invasive neoplastic cells at microscopic examination of the tumor remnants after surgery, following primary systemic therapy) in the breast.

• To evaluate the safety profiles of each treatment regimen, including pre-operative (neoadjuvant) and post-operative (adjuvant) treatment (i.e., trastuzumab).

• To investigate the overall survival (OS), the time to clinical response (CR), time-to-response, disease-free survival (DFS) and progression-free survival (PFS) for each treatment arm.

• To investigate the biomarkers that may be associated with primary and secondary efficacy endpoints in accordance with each treatment arm.

• To investigate the rate of breast conserving surgery for all patients with T2-3 tumours for whom mastectomy was planned at diagnosis.

Outcomes / endpoints

Primary endpoint:

Cardiac safety:

- Incidence of symptomatic cardiac events as assessed by the Investigator (Grade 3, 4 or 5 symptomatic LVSD)
- Clinically significant LVEF declines over the course of the neoadjuvant period (LVEF decline of ≥10% from baseline and to a value of <50%)

Secondary endpoints:

pCR (key secondary endpoint): The main efficacy endpoint was pCR rate in the breast, evaluated after six cycles of treatment and surgery or following withdrawal from the study, whichever occurred sooner. pCR was defined at the time of surgery and the rate is the proportion of the ITT population that achieved a pCR. A 95% confidence interval (CI) was calculated around the observed pCR rate for each treatment arm in order to show the variability associated with the point estimate. A pCR assessment was considered invalid if response to 'Microscopic assessment of primary tumor' is related to invasive carcinoma only (i.e., 'Associated with invasive carcinoma' or 'Distant from invasive carcinoma' ticked).

Clinical response rate: Tumour response was defined as complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD) and was identified as per local practice. Clinical response rate was defined as the proportion of patients who achieve a response of CR or PR at any time pre-surgery. Tumour response was assessed at each cycle, between Days 15-21 or on Study Day 1 of the next cycle.

Time to clinical response: Time to clinical response was the time from the date of first dose received to the first date of assessment of clinical response.

Breast conserving surgery rate: This was defined as the proportion of patients who achieved breast conserving surgery out of the ITT population without inflammatory breast cancer (these patients received mastectomy irrespective of their response to neoadjuvant treatment).

Overall survival (OS): This was defined as the time from randomization to the date of death from any cause. Patients who were alive or lost to follow-up were censored at the last known alive date. Patients with no post-baseline information were censored at the date of randomization plus one day.

Disease-free survival (DFS): This was defined as the time from the first date of no disease (i.e., date of surgery) to the first documentation of PD or death. Any evidence of contralateral disease in situ was not considered as PD. DFS was described separately in patients who achieved a pCR from those who did not. DFS was also described for the overall ITT population. Patients who were withdrawn from the study without documented PD were censored at the date of the last assessment when the patient was known to be disease-free.

Progression-free survival (PFS): This was defined as the time from the date of randomization to the first documentation of PD or death. Patients who were withdrawn from the study without documented PD were censored at the date of the last assessment when the patient was known to be free from PD.

Patients without post-baseline assessments but known to be alive were censored at the time of randomization plus one day.

Secondary safety endpoints:

- Incidence of symptomatic cardiac events and asymptomatic LVEF events
- LVEF measures over the course of the study
- Incidence and severity of AEs and SAEs
- Laboratory test abnormalities.

Explorative endpoints: Evaluation of biomarkers

Sample size

The sample size was based on the primary (safety) endpoint. Approximately 75 patients per arm were planned to be recruited into the study (225 in all).

Randomisation

Eligible patients were randomized via interactive voice response system (IVRS) at a central randomization center. Patients were randomly assigned using dynamic allocation to Arm A, B or C, and stratified by:

a) Breast cancer type: operable (T2-3, N0-1, M0), locally advanced (T2-3, N2 or N3, M0; T4a-c, any N, M0) and inflammatory (T4d, any N, M0) breast cancer

b) Hormonal receptor status: hormone receptor positive (ER+ and/ or PR+) versus negative (ER- and PR-).

Treatment was started within five working days after randomization.

Blinding (masking)

This was an open-label study.

Statistical methods

The safety population included patients who received any amount of study medication. Patients were assigned to treatment groups as treated.

Intent to Treat (ITT) Population consisted in all patients randomized, regardless of whether they received any study medication, were included in in the ITT population. Patients were assigned to treatment groups as randomized for analysis purposes. All efficacy outputs were produced for the ITT population.

Formal hypothesis testing was not planned. For pCR (the main efficacy endpoint) the approximate expected pCR rates were: Arm A: 50%, Arm B: 45% and Arm C: 40%. With the planned sample size, if these response rates were observed, the minimum true efficacy (lower bound of exact 95% confidence interval) of the estimates would be approximately A: 38.9% B: 33.8% C: 28.9%.

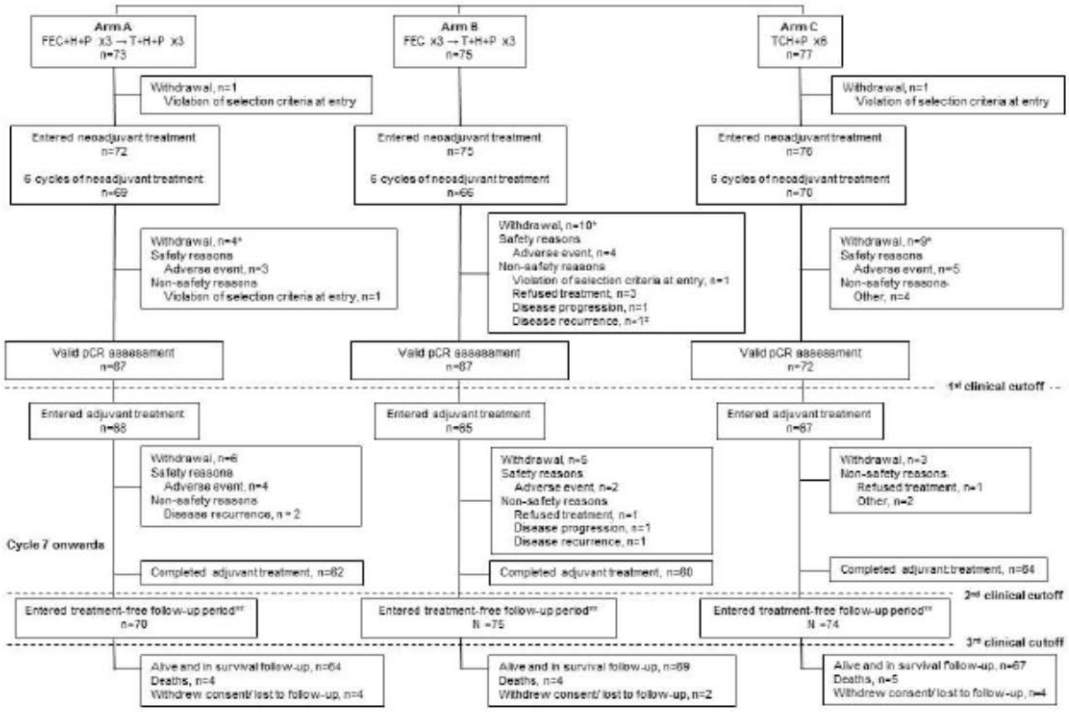
For the assessment of incidence of symptomatic left ventricular systolic dysfunction (LVSD), if the true underlying incidence was 3%, the probability of observing more than five such events in a treatment arm was 0.025.

Secondary endpoints were calculated and summarized for descriptive purposes only. Clinical response rate and the proportion achieving BCS in each treatment arm were tabulated, together with their associated 95% CIs. The Kaplan-Meier approach was used to estimate median time to clinical response

for each treatment arm. The Cox proportional hazards model, stratified by, operable, locally advanced, inflammatory breast cancer and oestrogen and or progesterone receptor positivity was used to estimate the Hazard Ratio (HR, i.e., the magnitude of treatment effect) and its 95% CI, for descriptive purposes only.

Results

Participant flow



*Patients could withdraw from neoadjuvant treatment, but still have on-study surgery and enter adjuvant treatment; 'Other' and 'Refused treatment' withdrawals include 'Withdrew consent'. **Includes all patients, i.e., those who withdrew during neoadjuvant and adjuvant periods, as well as those who completed study treatment)

Figure 5: Patient disposition

Recruitment

Patients were recruited at 44 centres across 19 countries (Bahamas, Bosnia and Herzegovina, Brazil, Canada, Croatia, Germany, Great Britain, Italy, Mexico, New Zealand, Portugal, Republic of China, Republic of Korea, Republic of Serbia, Romania, South Africa, Spain, Sweden, Switzerland). The period of trial was 26 November 2009 to 21 June 2011 (Clinical cut off).

Conduct of the study

Protocol amendment

The protocol was amended once for the following reasons:

- Protocol requirement for a mammogram between Study Day -14 and start of treatment: Extension of the window for the mammogram to be performed in screening period (from 14 days prior start of treatment to up to 42 days prior to the start of treatment) has been made to remove the need for a second 'study' mammogram if patient has recently received a mammogram as part of standard practice. In addition, centres were able to use MRI in place of mammography according to local practice.
- To provide information on the 'Emergency Medical Call Centre Help Desk' for medical emergencies outside regular business hours.

- To clarify schedule of ECG assessments in treatment period of study
- To provide information on Suspected Unexpected Serious Adverse Reactions (SUSAR) reporting.
- To clarify need for clinical breast exam and mammogram at end of Cycle 6 and prior to surgery.
- Clarification of CBC assessment schedule by treatment arm in neoadjuvant period of study.
- Clarification that Steering Committee will also look at key safety outputs from the neoadjuvant portion of the study.
- To clarify that investigators may adjust dose of study medications based upon small changes in body weight or body surface area.
- Clarification of modifications of dosing of non-investigational medicinal products (IMPs; i.e., docetaxel, carboplatin, 5-Fluorouracil, epirubicin and cyclophosphamide)

Protocol Deviations

Major Violations

More patients in Arm A reported an inclusion criteria violation (14%, vs 5% in Arm B and 7% in Arm C), all of which were designated as major violations. The most commonly reported inclusion criteria violation was a missing pregnancy test result (there were no positive pregnancy test results); all of these patients did have a baseline pregnancy test performed, but this was done outside the allowed time window. Other inclusion violations occurred for a variety of reasons, with no notable difference across arms for any individual reason. Three patients in Arm A entered the study with a primary tumor < 2 cm in diameter. One patient in Arm A entered the study and received the first cycle of treatment, despite not having confirmed HER2-positive breast cancer; this patient's tumor was IHC 0/1+, and HER2-positivity was not determined by FISH. The patient (who remained in the study at the investigator's discretion, until surgery was complete) was subsequently withdrawn on Study Day 191, for this reason. In addition, one patient in Arm C did not have the eCRF page filled in for FFPE tissue availability, and so was reported as not having tissue available for HER2 testing; however, this patient was tested and was found to be IHC 3+ and HER2-positive by FISH. One patient in Arm B and two patients in Arm C entered the study with a baseline LVEF reading of < 55%.

One patient in Arm B violated the criterion excluding patients with metastatic disease or bilateral breast cancer, since they were determined to have inflammatory metastatic breast cancer, and had presented with lung metastasis during screening. This patient was withdrawn on Study Day 24 for this reason. Approximately one quarter of patients in each treatment arm reported at least one on study protocol violation. The most common on-study violation was "patient safety compromised", reported in 15%, 20% and 12 % of patients across Arms A, B and C, respectively. This category included patients for whom tumor assessments/CBE, LVEF measurement, or hematology evaluations were omitted for at least one scheduled assessment, as well as patients who received an incorrect dose of study treatment.

Minor violations

More patients in Arm A reported an exclusion criteria violation (12%, vs 5% in Arm B and 8% in Arm C): all but the above noted case of metastatic disease, were minor violations. The majority of these were due to impaired liver function, as indicated by laboratory assessments.

Baseline data

Table 12: Demographic data and baseline characteristics

Protocol(s): BO22280
Analysis: SAFETY (BY TREATMENT RECEIVED) Center: ALL CENTERS
Snapshot Date: 01SEP2011 Clinical Cut-Off Date: 21JUN2011

	Total N = 223	FEC+P+T x3/ DOC+P+T x 3 N = 72	FEC x3/ DOC+P+T x 3 N = 75	TCH+P x6 N = 76
Sex				
FEMALE	223 (100%)	72 (100%)	75 (100%)	76 (100%)
n	223	72	75	76
Race				
BLACK	9 (4.0%)	4 (5.6%)	3 (4.0%)	2 (2.6%)
CAUCASIAN	171 (76.7%)	55 (76.4%)	52 (69.3%)	64 (84.2%)
ORIENTAL	40 (17.9%)	12 (16.7%)	18 (24.0%)	10 (13.2%)
OTHER	3 (1.3%)	1 (1.4%)	2 (2.7%)	-
n	223	72	75	76
Age (years)				
Mean	50.2	49.4	50.5	50.5
SD	10.87	11.41	10.70	10.62
SEM	0.73	1.35	1.24	1.22
Median	49.0	49.0	49.0	50.0
Min-Max	24 - 81	27 - 77	24 - 75	30 - 81
n	223	72	75	76
Age groups (years)				
<65	197 (88.3%)	62 (86.1%)	66 (88.0%)	69 (90.8%)
>=65	26 (11.7%)	10 (13.9%)	9 (12.0%)	7 (9.2%)
n	223	72	75	76
Weight at baseline (kg)				
Mean	67.3	65.6	66.6	69.6
SD	14.06	12.89	13.14	15.76
SEM	0.94	1.52	1.52	1.81
Median	65.0	63.3	64.9	66.5
Min-Max	42 - 128	44 - 111	42 - 112	45 - 128
n	223	72	75	76
Height at screening (cm)				
Mean	160.6	159.8	161.2	160.8
SD	7.65	7.15	7.97	7.81
SEM	0.52	0.85	0.93	0.90
Median	160.0	159.0	162.0	160.0
Min-Max	135 - 180	147 - 175	146 - 180	135 - 178
n	220	70	74	76
Female Reproductive Status				
POSTMENOPAUSAL	92 (41.3%)	24 (33.3%)	31 (41.3%)	37 (48.7%)
SURGICALLY STERIL.	35 (15.7%)	13 (18.1%)	11 (14.7%)	11 (14.5%)
WITH CONT. PROT.	96 (43.0%)	35 (48.6%)	33 (44.0%)	28 (36.8%)
n	223	72	75	76
Smoking Status				
CURRENT SMOKER	32 (14.3%)	8 (11.1%)	10 (13.3%)	14 (18.4%)
NEVER SMOKED	160 (71.7%)	53 (73.6%)	56 (74.7%)	51 (67.1%)
PAST SMOKER	31 (13.9%)	11 (15.3%)	9 (12.0%)	11 (14.5%)
n	223	72	75	76
Baseline ECOG Status				
0	198 (89.2%)	65 (91.5%)	66 (88.0%)	67 (88.2%)
1	24 (10.8%)	6 (8.5%)	9 (12.0%)	9 (11.8%)
n	222	71	75	76

n represents number of patients contributing to summary statistics.
Percentages are based on n (number of valid values). Percentages not calculated if n < 10.
DM11 05SEP2011:09:06:13
Source: t_dm11_s

Table 13: History of breast cancer and HER2 status

t_dm11_db_01 History of Breast Cancer and HER2 Status
Protocol(s): BO22280
Analysis: ITT (BY TREATMENT RANDOMIZED) Center: ALL CENTERS
Snapshot Date: 01SEP2011 Clinical Cut-Off Date: 21JUN2011

	Total N = 225	FEC+P+T x 3/ DOC+P+T x 3 N = 73	FEC x 3/ DOC+P+T x 3 N = 75	TCH+P x 6 N = 77
Estrogen receptor (ER) status				
ESTROGEN RECEPTOR NEGATIVE	118 (52.4%)	37 (50.7%)	44 (58.7%)	37 (48.1%)
ESTROGEN RECEPTOR POSITIVE	106 (47.1%)	36 (49.3%)	31 (41.3%)	39 (50.6%)
UNKNOWN	1 (0.4%)	-	-	1 (1.3%)
n	225	73	75	77
Progesterone receptor (PgR) status				
PROGESTERONE RECEPTOR NEGATIVE	143 (63.6%)	44 (60.3%)	52 (69.3%)	47 (61.0%)
PROGESTERONE RECEPTOR POSITIVE	82 (36.4%)	29 (39.7%)	23 (30.7%)	30 (39.0%)
n	225	73	75	77
Breast cancer type				
INFLAMMATORY	13 (5.8%)	5 (6.8%)	4 (5.3%)	4 (5.2%)
LOCALLY ADVANCED	56 (24.9%)	15 (20.5%)	17 (22.7%)	24 (31.2%)
OPERABLE	156 (69.3%)	53 (72.6%)	54 (72.0%)	49 (63.6%)
n	225	73	75	77
ER/PgR Status				
NEGATIVE	111 (49.3%)	34 (46.6%)	40 (53.3%)	37 (48.1%)
POSITIVE	114 (50.7%)	39 (53.4%)	35 (46.7%)	40 (51.9%)
n	225	73	75	77

n represents number of patients contributing to summary statistics.
Percentages are based on n (number of valid values). Percentages not calculated if n < 10.
ER/PgR Positive defined as ER positive and/or PgR positive. ER/PgR negative defined as ER negative and PgR negative
DM11 05SEP2011:09:29:47
Abridged from: page 200

t_dm11_db_01 History of Breast Cancer and HER2 Status
Protocol(s): BO22280
Analysis: ITT (BY TREATMENT RANDOMIZED) Center: ALL CENTERS
Snapshot Date: 01SEP2011 Clinical Cut-Off Date: 21JUN2011

	Total N = 225	FEC+P+T x 3/ DOC+P+T x 3 N = 73	FEC x 3/ DOC+P+T x 3 N = 75	TCH+P x 6 N = 77
Breast cancer type				
INFLAMMATORY	13 (5.8%)	5 (6.8%)	4 (5.3%)	4 (5.2%)
LOCALLY ADVANCED	56 (24.9%)	15 (20.5%)	17 (22.7%)	24 (31.2%)
OPERABLE	156 (69.3%)	53 (72.6%)	54 (72.0%)	49 (63.6%)
n	225	73	75	77
ER/PgR Status				
NEGATIVE	111 (49.3%)	34 (46.6%)	40 (53.3%)	37 (48.1%)
POSITIVE	114 (50.7%)	39 (53.4%)	35 (46.7%)	40 (51.9%)
n	225	73	75	77
Erythema				
<=1/3 OF BREAST	5 (41.7%)	1	2	2
> 1/3 OF BREAST	5 (41.7%)	3	1	1
NO	2 (16.7%)	1	-	1
n	12	5	3	4
Edema				
<=1/3 OF BREAST	2 (16.7%)	-	1	1
> 1/3 OF BREAST	5 (41.7%)	3	1	1
NO	5 (41.7%)	2	1	2
n	12	5	3	4
IHC result				
++	8 (3.6%)	5 (6.8%)	1 (1.3%)	2 (2.6%)
+++	216 (96.0%)	67 (91.8%)	74 (98.7%)	75 (97.4%)
0/+	1 (0.4%)	1 (1.4%)	-	-
n	225	73	75	77
FISH result				
NEGATIVE	3 (1.3%)	-	1 (1.3%)	2 (2.6%)
NK	11 (4.9%)	4 (5.5%)	5 (6.7%)	2 (2.6%)
POSITIVE	211 (93.8%)	69 (94.5%)	69 (92.0%)	73 (94.8%)
n	225	73	75	77

n represents number of patients contributing to summary statistics.
Percentages are based on n (number of valid values). Percentages not calculated if n < 10.
ER/PgR Positive defined as ER positive and/or PgR positive. ER/PgR negative defined as ER negative and PgR negative
DM11 05SEP2011:09:29:47 (2 of 3)

t_dm11_db_01 History of Breast Cancer and HER2 Status
Protocol(s): BO22280
Analysis: ITT (BY TREATMENT RANDOMIZED) Center: ALL CENTERS
Snapshot Date: 01SEP2011 Clinical Cut-Off Date: 21JUN2011

	Total N = 225	FEC+P+T x 3/ DOC+P+T x 3 N = 73	FEC x 3/ DOC+P+T x 3 N = 75	TCH+P x 6 N = 77
IHC / FISH result				
IHC +++/FISH NEGATIVE	3 (1.3%)	-	1 (1.3%)	2 (2.6%)
IHC +++/FISH NK	10 (4.4%)	3 (4.1%)	5 (6.7%)	2 (2.6%)
IHC +++/FISH POSITIVE	203 (90.2%)	64 (87.7%)	68 (90.7%)	71 (92.2%)
IHC ++/FISH POSITIVE	8 (3.6%)	5 (6.8%)	1 (1.3%)	2 (2.6%)
IHC 0/+/FISH NK	1 (0.4%)	1 (1.4%)	-	-
n	225	73	75	77

n represents number of patients contributing to summary statistics.
Percentages are based on n (number of valid values). Percentages not calculated if n < 10.
ER/PgR Positive defined as ER positive and/or PgR positive. ER/PgR negative defined as ER negative and PgR negative
DM11 05SEP2011:09:29:47 (3 of 3)

Numbers analysed

Table 14: Analysis populations

Protocol: BO22280
Analysis: All Patients
Snapshot Date: 01SEP2011 Clinical Cut-Off Date: 21JUN2011

	FEC+P+T x3/ DOC+P+T x3	FEC x3/ DOC+P+T x3	TCH+P x6
No. of Patients Randomized (ITT population)			
n	73	75	77
No. of Patients who Received Randomized Treatment	72 (98.6 %)	75 (100.0 %)	76 (98.7 %)
No. of Patients who Received no Treatment	1 (1.4 %)	0 (0.0 %)	1 (1.3 %)
Actual Treatment Received (SAP)			
n	72	75	76
Actually Received Randomized Treatment[*]	72 (100.0 %)	75 (100.0 %)	76 (100.0 %)

ITT = Intent-to-Treat Population. SAP = Safety Analysis Population (includes patients receiving any study medication)
All percentages are based on the number of patients randomized, other than [*] which are out of 'Actual Treatment Received'

Program : $PROD/cdp11450/bo22280/t_fapop.sas / Output : $PROD/cdp11450/j22280a/reports/t_fapop_a.out
02SEP2011 19:54 Page 1 of 1
Source: t_fapop_a

Outcomes and estimation

Safety results are presented under the section on clinical safety. Results on Overall survival (OS), Disease-free survival (DFS), and Progression-free survival (PFS) are not mature.

Secondary endpoints

pCR (key secondary endpoint)

Table 15: Pathological complete response rate

Protocol: BO22280
Analysis: ITT (By Treatment Randomized)
Snapshot Date: 01SEP2011 Clinical Cut-Off Date: 21JUN2011

	FEC+P+T x3/ DOC+P+T x3 (N=73)	FEC x3/ DOC+P+T x3 (N=75)	TCH+P x6 (N=77)
Responders[1]	45 (61.6 %)	43 (57.3 %)	51 (66.2 %)
Non-Responders	28 (38.4 %)	32 (42.7 %)	26 (33.8 %)
95% CI for Response Rates[2]	[49.5; 72.8]	[45.4; 68.7]	[54.6; 76.6]

[1] Responders are the patients who achieved pCR and non responders are the patients who did not achieve pCR or assessment is invalid or missing
[2] 95% CI for one sample binomial using Pearson-Clopper method

Clinical response rate

Table 16: Clinical response rate (Best overall response) during the neoadjuvant period

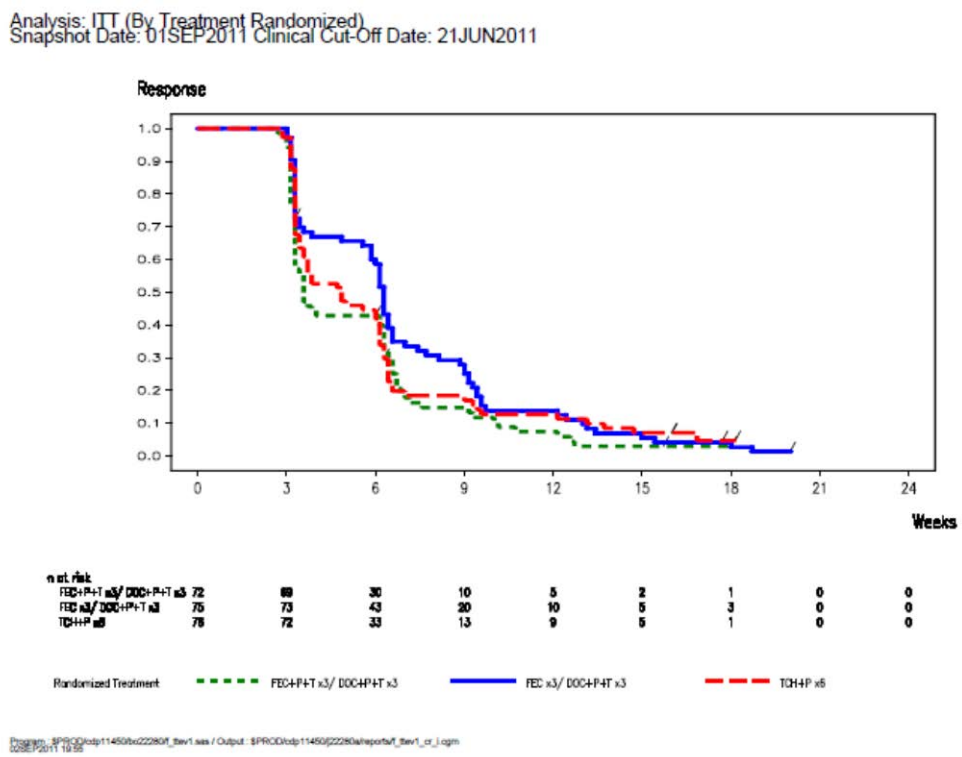
Protocol: BO22280
Analysis: ITT (By Treatment Randomized)
Snapshot Date: 01SEP2011 Clinical Cut-Off Date: 21JUN2011

	FEC+P+T x3/ DOC+P+T x3 (N=73)	FEC x3/ DOC+P+T x3 (N=75)	TCH+P x6 (N=77)
Responders*	67 (91.8 %)	71 (94.7 %)	69 (89.6 %)
Non-Responders	6 (8.2 %)	4 (5.3 %)	8 (10.4 %)
95% CI for Clinical Response Rate**	[83.0; 96.9]	[86.9; 98.5]	[80.6; 95.4]
Complete response (CR)	37 (50.7 %)	21 (28.0 %)	31 (40.3 %)
95% CI for Clinical Response Rate**	[38.7; 62.6]	[18.2; 39.6]	[29.2; 52.1]
Partial response (PR)	30 (41.1 %)	50 (66.7 %)	38 (49.4 %)
95% CI for Clinical Response Rate**	[29.7; 53.2]	[54.8; 77.1]	[37.8; 61.0]
Stable disease (SD)	3 (4.1 %)	1 (1.3 %)	5 (6.5 %)
95% CI for Clinical Response Rate**	[0.9; 11.5]	[0.0; 7.2]	[2.1; 14.5]
Progressive disease (PD)	0 (0.0 %)	1 (1.3 %)	0 (0.0 %)
95% CI for Clinical Response Rate**	[0.0; 4.9]	[0.0; 7.2]	[0.0; 4.7]
Unable to Assess (UA)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)
95% CI for Clinical Response Rate**	[0.0; 4.9]	[0.0; 4.8]	[0.0; 4.7]
Missing (no response assessment)	3 (4.1 %)	2 (2.7 %)	3 (3.9 %)

* Responders are the patients who achieved an overall response of CR or PR at any time during the neoadjuvant period. All other patients are classed as non responders
** 95% CI for one sample binomial using Pearson-Clopper method
Clinical response is based on the patient's best overall response during the neoadjuvant period

Time to clinical response

Median time to clinical response was shortest in Arm A (3.6 weeks) followed by Arm C (4.9 weeks) and then Arm B (6.9 weeks). However, the range in time to response was wide (between 1 and 18-20 weeks across arms).



Source: f_ttev1_cr_i

Figure 6: Kaplan-Meier plot of time to clinical response (weeks) in the TRYPHAENA study

Breast conserving surgery rate

Table 17: Patients achieving breast conserving surgery (BCS), ITT patients with T2-3 tumours for whom mastectomy was planned

Protocol: BO22280
Analysis: ITT (By Treatment Randomized)
Snapshot Date: 01SEP2011 Clinical Cut-Off Date: 21JUN2011

	FEC+P+T x3/ DOC+P+T x3 (N=46)	FEC x3/ DOC+P+T x3 (N=36)	TCH+P x6 (N=37)
BCS Achieved [1]	10 (21.7 %)	6 (16.7 %)	10 (27.0 %)
BCS Not Achieved [2]	36 (78.3 %)	30 (83.3 %)	27 (73.0 %)
95% CI for BCS Achieved*	[10.9; 36.4]	[6.4; 32.8]	[13.8; 44.1]
[1] Quadrantectomy	6 (13.0 %)	1 (2.8 %)	4 (10.8 %)
[1] Lumpectomy	4 (8.7 %)	5 (13.9 %)	6 (16.2 %)
[2] Mastectomy	33 (71.7 %)	26 (72.2 %)	23 (62.2 %)
[2] Missing/No Surgery	3 (6.5 %)	4 (11.1 %)	4 (10.8 %)
[3] Sentinel Node Biopsy	8 (17.4 %)	6 (16.7 %)	8 (21.6 %)
[3] Axillary Surgical Resection	40 (87.0 %)	29 (80.6 %)	29 (78.4 %)
[3] Other	1 (2.2 %)	2 (5.6 %)	1 (2.7 %)

* 95% CI for one sample binomial using Pearson-Clopper method
[1] includes quadrantectomy and lumpectomy
[2] includes mastectomy and missing/no surgery done
[3] includes surgeries other than mastectomy and breast conserving surgeries
If patients undergo both mastectomy and breast conserving surgery then patient is only counted under mastectomy.
Patients for whom planned surgery was not mastectomy or is missing are excluded from this table.
Percentages are based on mastectomy planned (n)
Patients may undergo more than one type of surgery, hence no. of patients may not add up to no. of patients in the treatment group

Comparison across trials

Table 18: Baseline Disease Characteristics: NEOSPHERE and TRYPHAENA (ITT Population)

Study Number	WO20697	BO22280
	N = 417	N = 225
Breast Cancer Stage/Type		
Inflammatory	29 (7.0%)	13 (5.8%)
Locally advanced	134 (32.1%)	56 (24.9%)
Operable	254 (60.9%)	156 (69.3%)
n	417	225
Histological Tumor Grade		
Anaplastic	1 (0.2%)	-
Moderately differentiated	123 (29.5%)	94 (41.8%)
Poorly differentiated	137 (32.9%)	78 (34.7%)
Unknown	146 (35.0%)	46 (20.4%)
Well differentiated	10 (2.4%)	7 (3.1%)
n	417	225
Estrogen Receptor Status		
Estrogen receptor negative	230 (55.2%)	118 (52.4%)
Estrogen receptor positive	186 (44.6%)	106 (47.1%)
Receptor status not known	1 (0.2%)	1 (0.4%)
n	417	225
Progesterone Receptor Status		
Progesterone receptor negative	278 (66.7%)	143 (63.6%)
Progesterone receptor positive	138 (33.1%)	82 (36.4%)
Receptor status not known	1 (0.2%)	-
n	417	225
Hormone Receptor Positivity		
Estrogen and progesterone negative	219 (52.6%)	111 (49.3%)
Estrogen and/or progesterone positive	197 (47.4%)	114 (50.7%)
n	416	225
HER2 Status IHC		
0/1+	-	1 (0.4%)
2+	31 (7.5%)	8 (3.6%)
3+	380 (92.5%)	216 (96.0%)
n	411	225
HER2 Status FISH		
NK	3 (3.2%)	11 (4.9%)
Positive	90 (96.8%)	211 (93.8%)
Negative	-	3 (1.3%)
n	93	225
HER2 Status IHC/FISH Combined		
- /FISH positive	6 (1.4%)	-
IHC 2+/FISH positive	31 (7.4%)	8 (3.6%)

Study Number	WO20697	BO22280
	N = 417	N = 225
IHC 3+ [a]	324 (77.7%)	-
IHC 3+/FISH NK [b]	3 (0.7%)	10 (4.4%)
IHC 3+/FISH positive [a]	53 (12.7%)	203 (90.2%)
Location of Primary Tumour		
Left	211 (50.6%)	120 (53.3%)
Right	206 (49.4%)	105 (46.7%)
n	417	225

FISH: Fluorescence insitu hybridization; HER2: Human epidermal growth factor receptor 2; IHC: Immunohistochemistry; ND: Not done; NK: Not known;
[a] For NEOSPHERE, FISH testing was not necessary if the patient was IHC3+
[b] "IHC3+" alone means that only IHC testing was performed, "IHC3+ / FISH NK" means FISH was also performed but results were not valid or not interpretable

Pathological complete response

pCR by different definitions

Definitions are summarised in Table 1.

Table 19: pCR rates according to different definitions: NEOSPHERE and TRYPHAENA

	NEOSPHERE				TRYPHAENA		
	T+D	Ptz+T+D	Ptz+T	Ptz+D	Ptz+T+FEC/ Ptz+T+D	FEC/ Ptz+T+D	Ptz+TCH
bpCR, ypT0/is (%) [95% CI]	31 (29.0%) [20.6; 38.5]	49 (45.8%) [36.1; 55.7]	18 (16.8%) [10.3; 25.3]	23 (24.0%) [15.8; 33.7]	45 (61.6%) [49.5; 72.8]	43 (57.3%) [45.4; 68.7]	51 (66.2%) [54.6; 76.6]
p-value from CMH		0.0094 (vs. T+D)	0.0198 (vs. T+D)	0.0010 (vs. Ptz+T+D)			
p-value (with Simes corr. for CMH test) #		0.0141 (vs. T+D)	0.0198 (vs. T+D)	0.0030 (vs. Ptz+T+D)	-	-	-
tpCR, ypT0/is ypN0 (%) [95% CI]	23 (21.5%) [14.1; 30.5]	42 (39.3%) [30.0; 49.2]	12 (11.2%) [5.9; 18.8]	17 (17.7%) [10.7; 26.8]	41 (56.2%) [44.1; 67.8]	41 (54.7%) [42.7; 66.2]	49 (63.6%) [51.9; 74.3]
GBG pCR, ypT0 ypN0 (%) [95% CI]	13 (12.1%) [6.6; 19.9]	35 (32.7%) [24.0; 42.5]	6 (5.6%) [2.1; 11.8]	13 (13.5%) [7.4; 22.0]	37 (50.7%) [38.7; 62.6]	34 (45.3%) [33.8; 57.3]	40 (51.9%) [40.3; 63.5]

# Hypothesis testing at alpha level of 0.2
CMH= Cochran-Mantel-Haenszel test; pCR=pathological complete response;
Source: For NEOSPHERE: t_ovpcr_l ; for TRYPHAENA: t_ovpcr_l .

pCR by disease stage/type

Table 20: Summary of pCR rates by disease stage/type and according to different definitions: NEOSPHERE and TRYPHAENA

	NEOSPHERE				TRYPHAENA		
	T+D	Ptz+T+D	Ptz+T	Ptz+D	Ptz+T+FEC/ Ptz+T+D	FEC/ Ptz+T+D	Ptz+TCH
Overall							
N	107	107	107	96	73	75	77
N (%) achieving bpCR	31 (29.0%)	49 (45.8%)	18 (16.8%)	23 (24.0%)	45 (61.6%)	43 (57.3%)	51 (66.2%)
N (%) achieving tpCR	23 (21.5%)	42 (39.3%)	12 (11.2%)	17 (17.7%)	41 (56.2%)	41 (54.7%)	49 (63.6%)
N (%) achieving GBG pCR	13 (12.1%)	35 (32.7%)	6 (5.6%)	13 (13.5%)	37 (50.7%)	34 (45.3%)	40 (51.9%)
Operable breast cancer							
N	64	65	65	60	53	54	49
N (%) achieving bpCR	15 (23.4%)	31 (47.7%)	11 (16.9%)	16 (26.7%)	34 (64.2%)	29 (53.7%)	32 (65.3%)
N (%) achieving tpCR	12 (18.8%)	26 (40.0%)	9 (13.8%)	14 (23.3%)	32 (60.4%)	28 (51.9%)	31 (63.3%)
N (%) achieving GBG pCR	5 (7.8%)	22 (33.8%)	4 (6.2%)	10 (16.7%)	28 (52.8%)	23 (42.6%)	27 (55.1%)
LABC							
N	36	32	35	31	15	17	24
N (%) achieving bpCR	15 (41.7%)	14 (43.8%)	5 (14.3%)	5 (16.1%)	8 (53.3%)	13 (76.5%)	15 (62.5%)
N (%) achieving tpCR	10 (27.8%)	13 (40.6%)	2 (5.7%)	2 (6.5%)	8 (53.3%)	12 (70.6%)	14 (58.3%)
N (%) achieving GBG pCR	7 (19.4%)	12 (37.5%)	1 (2.9%)	2 (6.5%)	8 (53.3%)	10 (58.8%)	11 (45.8%)
IBC							
N	7	10	7	5	5	4	4
N (%) achieving bpCR	1 (14.3%	4 (40.0%)	2 (28.6%)	2 (40.0%)	3 (60.0%)	1 (25.0%)	4 (100%)
N (%) achieving tpCR	1 (14.3%)	3 (30.0%)	1 (14.3%)	1 (20.0%)	1 (20.0%)	1 (25.0%)	4 (100.0%)
N (%) achieving GBG pCR	1 (14.3%)	1 (10.0%)	1 (14.3%)	1 (20.0%)	1 (20.0%)	1 (25.0%)	2 (50.0%)

Source: for NEOSPHERE t_mpor02_bct_l , t_fpor03_bct_l , t_fpor03_gbg_bct_l ;
for TRYPHAENA t_mpor02_bct_l , t_fpor03_bct_l , t_fpor03_gbg_bct_l

pCR by hormone receptor status

Table 21: Summary of pCR rates by hormone receptor status and according to different definitions

	NEOSPHERE				TRYPHAENA		
	T+D	Ptz+T+D	Ptz+T	Ptz+D	Ptz+T+FEC/ Ptz+T+D	FEC/ Ptz+T+D	Ptz+TCH
Overall							
N	107	107	107	96	73	75	77
N (%) achieving bpCR	31 (29.0%)	49 (45.8%)	18 (16.8%)	23 (24.0%)	45 (61.6%)	43 (57.3%)	51 (66.2%)
N (%) achieving tpCR	23 (21.5%)	42 (39.3%)	12 (11.2%)	17 (17.7%)	41 (56.2%)	41 (54.7%)	49 (63.6%)
N (%) achieving GBG pCR	13 (12.1%)	35 (32.7%)	6 (5.6%)	13 (13.5%)	37 (50.7%)	34 (45.3%)	40 (51.9%)
Hormone Receptor Negative (ER and PgR negative)							
N	57	57	55	50	34	40	37
N (%) achieving bpCR	21 (36.8%)	36 (63.2%)	15 (27.3%)	15 (30.0%)	27 (79.4%)	26 (65.0%)	31 (83.8%)
N (%) achieving tpCR	17 (29.8%)	31 (54.4%)	11 (20.0%)	13 (26.0%)	25 (73.5%)	25 (62.5%)	30 (81.1%)
N (%) achieving GBG pCR	8 (14.0%)	28 (49.1%)	5 (9.1%)	11 (22.0%)	23 (67.6%)	19 (47.5%)	25 (67.6%)
Hormone Receptor Positive (ER- and/or PgR-positive)							
N	50	50	51	46	39	35	40
N (%) achieving bpCR	10 (20.0%)	13 (26.0%)	3 (5.9%)	8 (17.4%)	18 (46.2%)	17 (48.6%)	20 (50.0%)
N (%) achieving tpCR	6 (12.0%)	11 (22.0%)	1 (2.0%)	4 (8.7%)	16 (41.0%)	16 (45.7%)	19 (47.5%)
N (%) achieving GBG pCR	5 (10.0%)	7 (14.0%)	1 (2.0%)	2 (4.3%)	14 (35.9%)	15 (42.9%)	15 (37.5%)

Source: for NEOSPHERE t_rr_por02_hrt_l , t_fpor03_hrt_l and t_fpor03_gbg_hrt_l ;
for TRYPHAENA t_rr_por02_hrt_l , t_fpor03_hrt_l and t_fpor03_gbg_hrt_l

pCR by tumour and nodal stage

Table 22: Overview of pCR rates by trial treatment and tumour stage

t_fpcr04tnm_1 Overview of pCR Rates by Trial Treatment and Tumor Stage
Protocol: WO20697
Analysis: ITT (By Treatment Randomized)
Snapshot Date: 13AUG2012 Clinical Cut-Off Date: 09MAR2012

Tumor Stage	pCR Definiton		Trastuzumab + Docetaxel (N=107)	Trastuzumab + Pertuzumab + Docetaxel (N=107)	Trastuzumab + Pertuzumab (N=107)	Pertuzumab + Docetaxel (N=96)
T2	n		42	46	47	45
	ypTO/is	(%)	16(38.1%)	19(41.3%)	9(19.1%)	12(26.7%)
	ypTO/is ypNO	(%)	13(31.0%)	15(32.6%)	6(12.8%)	9(20.0%)
	ypTO ypNO	(%)	6(14.3%)	13(28.3%)	3(6.4%)	6(13.3%)
T3	n		38	32	37	32
	ypTO/is	(%)	6(15.8%)	19(59.4%)	7(18.9%)	8(25.0%)
	ypTO/is ypNO	(%)	4(10.5%)	17(53.1%)	5(13.5%)	7(21.9%)
	ypTO ypNO	(%)	2(5.3%)	15(46.9%)	2(5.4%)	6(18.8%)
T4	n		27	28	23	19
	ypTO/is	(%)	9(33.3%)	11(39.3%)	2(8.7%)	3(15.8%)
	ypTO/is ypNO	(%)	6(22.2%)	10(35.7%)	1(4.3%)	1(5.3%)
	ypTO ypNO	(%)	5(18.5%)	7(25.0%)	1(4.3%)	1(5.3%)

Percentages are based on subgroup n
"ypTO/is" - Elimination of all invasive disease in the breast (residual carcinoma in-situ acceptable)
"ypTO/is NO" - Elimination of all invasive disease in the breast (residual carcinoma in-situ acceptable) AND node negative at surgery
"ypTO NO" - Elimination of all disease (invasive and non-invasive) in the breast AND node negative at surgery

Program : $PROD/cdp11450/wo20697/t_fpcr04tnm.sas / Output : $PROD/cdp11450/120697l/reports/t_fpcr04tnm_1.out
05MAR2013 16:25 Page 1 of 1

Table 23: Overview of pCR rates by trial treatment and nodal stage

t_fpcr04node_1 Overview of pCR Rates by Trial Treatment and Nodal Stage
Protocol: WO20697
Analysis: ITT (By Treatment Randomized)
Snapshot Date: 13AUG2012 Clinical Cut-Off Date: 09MAR2012

Nodal Stage	pCR Definiton		Trastuzumab + Docetaxel (N=107)	Trastuzumab + Pertuzumab + Docetaxel (N=107)	Trastuzumab + Pertuzumab (N=107)	Pertuzumab + Docetaxel (N=96)
N0	n		32	31	32	28
	ypTO/is	(%)	8(25.0%)	17(54.8%)	5(15.6%)	6(21.4%)
	ypTO/is ypNO	(%)	6(18.8%)	16(51.6%)	4(12.5%)	5(17.9%)
	ypTO ypNO	(%)	1(3.1%)	13(41.9%)	1(3.1%)	4(14.3%)
N1	n		48	53	46	41
	ypTO/is	(%)	12(25.0%)	21(39.6%)	8(17.4%)	12(29.3%)
	ypTO/is ypNO	(%)	9(18.8%)	16(30.2%)	6(13.0%)	9(22.0%)
	ypTO ypNO	(%)	7(14.6%)	14(26.4%)	4(8.7%)	6(14.6%)
N2 or N3	n		27	22	29	27
	ypTO/is	(%)	11(40.7%)	11(50.0%)	5(17.2%)	5(18.5%)
	ypTO/is ypNO	(%)	8(29.6%)	10(45.5%)	2(6.9%)	3(11.1%)
	ypTO ypNO	(%)	5(18.5%)	8(36.4%)	1(3.4%)	3(11.1%)

Percentages are based on subgroup n
"ypTO/is" - Elimination of all invasive disease in the breast (residual carcinoma in-situ acceptable)
"ypTO/is NO" - Elimination of all invasive disease in the breast (residual carcinoma in-situ acceptable) AND node negative at surgery
"ypTO NO" - Elimination of all disease (invasive and non-invasive) in the breast AND node negative at surgery

Program : $PROD/cdp11450/wo20697/t_fpcr04node.sas / Output : $PROD/cdp11450/120697l/reports/t_fpcr04node_1.out
05MAR2013 16:25 Page 1 of 1

pCR by age

The great majority of patients in both studies were <65 years of age. Despite the small patient numbers in the age group > 65 years and regardless of the pCR definition used, consistent trends are seen for patients in both age groups compared with the overall population, i.e., a higher pCR rate in the Ptz+T+D arm compared with the T+D arm of the NEOSPHERE study.

Table 24: pCR by age group: NEOSPHERE and TRYPHAENA

	NEOSPHERE				TRYPHAENA		
	T+D n=107	Ptz+T+D n=107	Ptz+T n=108	Ptz+D n=94	Ptz+T+FEC/ Ptz+T+D	FEC/ Ptz+T+D	Ptz+TCH
Overall							
N	107	107	107	96	73	75	77
N (%) achieving bpCR	31 (29.0%)	49 (45.8%)	18 (16.8%)	23 (24.0%)	45 (61.6%)	43 (57.3%)	51 (66.2%)
N (%) achieving tpCR	23 (21.5%)	42 (39.3%)	12 (11.2%)	17 (17.7%)	41 (56.2%)	41 (54.7%)	49 (63.6%)
N (%) achieving GBG pCR	13 (12.1%)	35 (32.7%)	6 (5.6%)	13 (13.5%)	37 (50.7%)	34 (45.3%)	40 (51.9%)
< 65 years							
N	97	99	99	90	63	66	70
N (%) achieving bpCR	29 (29.9%)	45 (45.5%)	17 (17.2%)	22 (24.4%)	39 (61.9%)	35 (53.0%)	46 (65.7%)
N (%) achieving tpCR	21 (21.6%)	38 (38.4%)	11 (11.1%)	17 (18.9%)	35 (55.6%)	33 (50.0%)	44 (62.9%)
N (%) achieving GBG pCR	11 (11.3%)	31 (31.3%)	5 (5.1%)	13 (14.4%)	31 (49.2%)	30 (45.5%)	39 (55.7%)
≥ 65 years							
N	10	8	8	6	10	9	7
N (%) achieving bpCR	2 (20.0%)	4 (50.0%)	1 (12.5%)	1 (16.7%)	6 (60.0%)	8 (88.9%)	5 (71.4%)
N (%) achieving tpCR	2 (20.0%)	4 (50.0%)	1 (12.5%)	0	6 (60.0%)	8 (88.9%)	5 (71.4%)
N (%) achieving GBG pCR	2 (20.0%)	4 (50.0%)	1 (12.5%)	0	6 (60.0%)	4 (44.4%)	1 (14.3%)

Source: For NEOSPHERE t_fpcr03_mar_age65_i , t_fpcr03_age65_i , t_fpcr03_gbg_age65_i
For TRYPHAENA t_fpcr03_mar_age65_i , t_fpcr03_age65_i , t_fpcr03_gbg_age65_i

pCR by race

Table 25: pCR by race: NEOSPHERE and TRYPHAENA

	NEOSPHERE				TRYPHAENA		
	T+D n=107	Ptz+T+D n=107	Ptz+T n=108	Ptz+D n=94	Ptz+T+FEC/ Ptz+T+D	FEC/ Ptz+T+D	Ptz+TCH
Overall							
N	107	107	107	96	73	75	77
N (%) achieving bpCR	31 (29.0%)	49 (45.8%)	18 (16.8%)	23 (24.0%)	45 (61.6%)	43 (57.3%)	51 (66.2%)
N (%) achieving tpCR	23 (21.5%)	42 (39.3%)	12 (11.2%)	17 (17.7%)	41 (56.2%)	41 (54.7%)	49 (63.6%)
N (%) achieving GBG pCR	13 (12.1%)	35 (32.7%)	6 (5.6%)	13 (13.5%)	37 (50.7%)	34 (45.3%)	40 (51.9%)
White							
N	80	77	79	61	56	52	64
N (%) achieving bpCR	21 (26.3%)	36 (46.8%)	10 (12.7%)	9 (14.8%)	32 (57.1%)	28 (53.8%)	42 (65.6%)
N (%) achieving tpCR	15 (18.8%)	30 (39.0%)	6 (7.6%)	5 (8.2%)	29(51.8%)	28(53.8%)	40 (62.5%)
N (%) achieving GBG pCR	11 (13.8%)	24 (31.2%)	4 (5.1%)	4 (6.6%)	27 (48.2%)	22 (42.3%)	31 (48.4%)
Asian							
N	25	23	23	25	12	18	11
N (%) achieving bpCR	10 (40.0%)	11 (47.8%)	7 (30.4%)	11 (44.0%)	10 (83.3%)	13 (72.2%)	8 (72.7%)
N (%) achieving tpCR	8 (32.0%)	10 (43.5%)	6 (26.1%)	9 (36.0%)	9 (75.0%)	11 (61.1%)	8 (72.7%)
N (%) achieving GBG pCR	2 (8.0%)	9 (39.1%)	2 (8.7%)	6 (24.0%)	7 (58.3%)	10 (55.6%)	8(72.7%)
Black							
N	0	2	1	3	4	3	2
N (%) achieving bpCR	0	1 (50.0%)	0	0	3 (75.0%)	2 (66.7%)	1 (50.0%)
N (%) achieving tpCR	0	1 (50.0%)	0	0	3 (75.0%)	2 (66.7%)	1 (50.0%)
N (%) achieving GBG pCR	0	1 (50.0%)	0	0	3 (75.0%)	2 (66.7%)	1 (50.0%)
Other							
N	2	5	4	7	1	2	0
N (%) achieving bpCR	0	1 (20.0%)	1 (25.0%)	3 (42.9%)	0	0	0
N (%) achieving tpCR	0	1 (20.0%)	0	3 (42.9%)	0	0	0
N (%) achieving GBG pCR	0	1 (20.0%)	0	3 (42.9%)	0	0	0

Source: for NEOSPHERE t_fpcr03_mar_race_i , t_fpcr03_race_i , t_fpcr03_gbg_race_i;
For TRYPHAENA t_fpcr03_mar_race_i , t_fpcr03_race_i , and t_fpcr03_gbg_race_i

pCR by region

Table 26: pCR by region: NEOSPHERE and TRYPHAENA

	NEOSPHERE				TRYPHAENA		
	T+D n=107	Ptz+T+D n=107	Ptz+T n=108	Ptz+D n=94	Ptz+T+FEC/ Ptz+T+D	FEC/ Ptz+T+D	Ptz+TCH
Overall							
N	107	107	107	96	73	75	77
N (%) achieving bpCR	31 (29.0%)	49 (45.8%)	18 (16.8%)	23 (24.0%)	45 (61.6%)	43 (57.3%)	51 (66.2%)
N (%) achieving tpCR	23 (21.5%)	42 (39.3%)	12 (11.2%)	17 (17.7%)	41 (56.2%)	41 (54.7%)	49 (63.6%)
N (%) achieving GBG pCR	13 (12.1%)	35 (32.7%)	6 (5.6%)	13 (13.5%)	37 (50.7%)	34 (45.3%)	40 (51.9%)
Europe							
N	63	71	62	49	39	39	50
N (%) achieving bpCR	17 (27.0%)	33 (46.5%)	8 (12.9%)	8 (16.3%)	23 (59.0%)	20 (51.3%)	33 (66.0%)
N (%) achieving tpCR	12 (19.0%)	28 (39.4%)	4 (6.5%)	5 (10.2%)	20 (51.3%)	20 (51.3%)	32 (64.0%)
N (%) achieving GBG pCR	9 (14.3%)	24 (33.8%)	3 (4.8%)	4 (8.2%)	18 (46.2%)	16 (41.0%)	24 (48.0%)
Asia							
N	26	22	22	25	9	14	10
N (%) achieving bpCR	10 (38.5%)	10 (45.5%)	7 (31.8%)	11 (44.0%)	8 (88.9%)	10 (71.4%)	8 (80.0%)
N (%) achieving tpCR	8 (30.8%)	9 (40.9%)	6 (27.3%)	9 (36.0%)	7 (77.8%)	9 (64.3%)	8 (80.0%)
N (%) achieving GBG pCR	2 (7.7%)	8 (36.4%)	2 (9.1%)	6 (24.0%)	5 (55.6%)	8 (57.1%)	8 (80.0%)
North America							
N	5	5	10	8	9	7	5
N (%) achieving bpCR	0	3 (60.0%)	1 (10.0%)	2 (25.0%)	7 (77.8%)	3 (42.9%)	3 (60.0%)
N (%) achieving tpCR	0	2 (40.0%)	0	1 (12.5%)	7 (77.8%)	2 (28.6%)	3 (60.0%)
N (%) achieving GBG pCR	0	1 (20.0%)	0	1 (12.5%)	7 (77.8%)	2 (28.6%)	3 (60.0%)

Table continues

	NEOSPHERE				TRYPHAENA		
	T+D n=107	Ptz+T+D n=107	Ptz+T n=108	Ptz+D n=94	Ptz+T+FEC/ Ptz+T+D	FEC/ Ptz+T+D	Ptz+TCH
South America							
N	12	9	13	14	13	10	10
N (%) achieving bpCR	3 (25.0%)	3 (33.3%)	2 (15.4%)	2 (14.3%)	6 (46.2%)	6 (60.0%)	6 (60.0%)
N (%) achieving tpCR	2 (16.7%)	3 (33.3%)	2 (15.4%)	2 (14.3%)	6 (46.2%)	6 (60.0%)	5 (50.0%)
N (%) achieving GBG pCR	1 (8.3%)	2 (22.2%)	1(7.7%)	2(14.3%)	6 (46.2%)	4 (40.0%)	4 (40.0%)
Other							
N	1	0	0	0	3	5	2
N (%) achieving bpCR	1 (100.0%)	0	0	0	1 (33.3%)	4 (80.0%)	1 (50.0%)
N (%) achieving tpCR	1 (100.0%)	0	0	0	1 (33.3%)	4 (80.0%)	1 (50.0%)
N (%) achieving GBG pCR	1 (100.0%)	0	0	0	1 (33.3%)	4 (80.0%)	1 (50.0%)

Source: for NEOSPHERE t_fpcr03_mar_reg_i , t_fpcr03_reg_i , t_fpcr03_gbg_reg_i ;
For TRYPHAENA t_fpcr03_mar_reg_i , t_fpcr03_reg_i , t_fpcr03_gbg_reg_i

Clinical responses

Clinical responses were evaluated slightly differently in the NEOSPHERE and TRYPHAENA studies (see methods). To assist comparison between the studies, overall assessment of response (i.e., for breast and lymph nodes) based on CBE is provided for the two studies. Evaluation based on CBE is shown since this was scheduled at every cycle and in all patients in both studies and because CBE includes assessment of lymph nodes as well as the breast. In both studies the majority of patients achieved a clinical response (CR or PR) during the neoadjuvant period. Very few patients in either study experienced disease progression (PD) as their best response to neoadjuvant. However, some patients in the NEOSPHERE study (mainly patients in the Ptz+T arm) experienced disease progression during the neoadjuvant period after initially appearing to have stable disease. Only one patient in the TRYPHAENA study experienced disease progression during the neoadjuvant period. This patient, with LABC, was randomized to receive FEC/Ptz+T+D and experienced PD after one cycle of FEC (before any pertuzumab or trastuzumab had been given). Overall, clinical response rates and clinical CR rates were consistent with the pCR findings in the two studies, with numerically higher pCR rates occurring in the TRYPHAENA study and, within the NEOSPHERE study, the highest pCR rates occurring in the Ptz+T+D arm and the lowest in the Ptz+T arm.

Overall clinical response and clinical CR rates were also higher in the Ptz+T+D arm compared with the T+D arm of the NEOSPHERE study. Patients in the FEC/Ptz+T+D arm of the TRYPHAENA study were less likely to achieve a clinical CR than patients in the other two arms of this study. Patients in this treatment arm received less neoadjuvant pertuzumab and trastuzumab (three doses/cycles) than patients in the other two arms of the study (six doses/cycles), and these patients also started pertuzumab and trastuzumab later (Cycle 4, compared with Cycle 1 in the other two arms of the TRYPHAENA study).

Table 27: Summary of clinical response rates (by clinical examination): NEOSPHERE and TRYPHAENA

	NEOSPHERE				TRYPHAENA		
	T+D	Ptz+T+D	Ptz+T	Ptz+D	Ptz+T+FEC/ Ptz+T+D	FEC/ Ptz+T+D	Ptz+TCH
N[a]	97	100	98	88	73	75	77
Overall response (CR + PR)	79 (81.4%)	88 (88.0%)	65 (66.3%)	65 (73.9%)	67 (91.8%)	71 (94.7%)	69 (89.6%)
Best clinical response[b] CR	21 (21.6%)	25 (25.0%)	11 (11.2%)	14 (15.9%)	37 (50.7%)	21 (28.0%)	31 (40.3%)
PR	58 (59.8%)	63 (63.0%)	54 (55.1%)	51 (58.0%)	30 (41.1%)	50 (66.7%)	38 (49.4%)
SD	17 (17.5%)	12 (12.0%)	31 (31.6%)	23 (26.1%)	3 (4.1%)	1 (1.3%)	5 (6.5%)
PD	1 (1.0%)	0	2 (2.0%)	0	0	1 (1.3%)	0
Investigator determined progression during the neoadjuvant period	0[c]	1 (0.9%)[d]	8 (7.5%)[e]	2 (2.1%)[f]	0	1 (1.3%)	0

[a] N for NEOSPHERE excludes patients with missing data/unevaluable. In TRYPHAENA, patients with missing data or otherwise unevaluable are considered non-resonders

[b] Derived by the Sponsor based on investigator measurememts for NEOSPHERE; based on Investigator assessment of response for TRYPHAENA

[c] Progressive disease (PD) noted on CBE by the Sponsor, but was not noted by the investigator

[d] No increase was noted by CBE therefore best clinical response was calculated as stable disease, progressive disease was noted on mammography

[e] 8 patients had PD during the neoadjuvant period (4 based on X-ray/mammography, 2 on ultrasound, and 2 on CBE).

[f] 2 patients progressed on CBE after initial assessment of stable disease

Source: For NEOSPHERE t_ftr_bt_it_, t_rr2pd_i, l_bor1_bt_amd and l_tum1_pb_amd; For TRYPHAENA t_rrcre_i, t_rr2pd_i

Time to Clinical Response (PR/CR)

Table 28: Summary of time to first clinical response based on primary breast lesion: NEOSPHERE and TRYPHAENA

	NEOSPHERE				TRYPHAENA		
	T+D	Ptz+T+D	Ptz+T	Ptz+D	Ptz+T+FEC/ Ptz+T+D	FEC/ Ptz+T+D	Ptz+TCH
Number of patients included in analysis	99	101	102	91	70	73	74
Patients with a response	79 (79.8%)	89 (88.1%)	69 (67.6%)	65 (71.4%)	67 (95.7%)	71 (97.3%)	69 (93.2%)
Time to response (weeks)							
Median*	6.3	6.3	6.9	7.3	3.6	6.3	4.9
Range	3-13	3-13	3-13	3-13	3-18	3-20	3-18

*Kaplan-Meier estimates

Source: For NEOSPHERE t_ttev1_pbe_i and for TRYPHAENA: t_ttev_cr_i

Breast Conserving Surgery

Excluding patients with IBC (who according to current guidelines undergo mastectomy regardless of response to neoadjuvant therapy) the majority of patients in both studies had a mastectomy: 25.0%-33.0% of patients underwent BCS in the NEOSPHERE study and 32.9%-33.3% of patients in the TRYPHAENA study underwent BCS, regardless of original intent. Overall rates of BCS were similar in the NEOSPHERE study, although patients in the Ptz+D arm were slightly more likely to undergo BCS. Overall rates of BCS were similar in the three arms of the TRYPHAENA study.

Of the patients with T2-T3 disease for whom a mastectomy was planned in the NEOSPHERE study, 18.0%-31.7% actually underwent BCS. In the TRYPHAENA study, patients with T2-T3 disease for whom a mastectomy was planned were less likely to undergo BCS in the FEC/Ptz+T+D arm compared with the Ptz+T+FEC/Pt+T+D and Ptz+TCH arms of the study.

For the NEOSPHERE study, full details of the planned versus actual surgical procedures are provided, for the overall patient population, and split by treatment group. For TRYPHAENA, a listing of the planned and actual surgery for breast cancer is provided.

Table 29: Breast Conserving Surgery: NEOSPHERE and TRYPHAENA

	NEOSPHERE				TRYPHAENA		
	T+D	Ptz+T+D	Ptz+T	Ptz+D	Ptz+T+FEC/ Ptz+T+D	FEC/ Ptz+T+D	Ptz+TCH
Total number of patients	107	107	107	96	73	75	77
Total without IBC [a]	100	97	100	91	68	72	73
Total who underwent BCS [b]	25 (25.0%)	27 (27.8%)	26 (26.0%)	30 (33.0%)	23 (33.8%)	24 (33.3%)	24 (32.9%)
Number with T4 non-IBC tumors	20	18	16	14	6	8	15
T4 non-IBC who underwent BCS [c]	0	1 (5.6%)	1 (6.3%)	0	2 (33.3%)	1 (12.5%)	0
Number with T2-3 tumors	80	78	84	77	61	63	58
T2-3 tumors who underwent BCS [d]	25 (31.3%)	26 (33.3%)	25 (29.8%)	30 (39.0%)	21 (34.4%)	23 (36.5%)	24 (41.4%)
Number with T2-T3 tumors and planned mastectomy	62	56	61	60	46	36	37
T2-3, planned mastectomy, underwent BCS [e]	14 (22.6%)	13 (23.2%)	11 (18.0%)	19 (31.7%)	10 (21.7 %)	6 (16.7 %)	10 (27.0 %)

[a] Mastectomy required for IBC regardless of response to therapy
[b] Expressed as a percentage of patients without IBC
[c] Expressed as a percentage of patients with T4 non-IBC tumors
[d] Expressed as a percentage of patients with T2-3 tumors
[e] Expressed as a percentage of patients with T2-3 tumors and planned mastectomy

Source: for NEOSPHERE - t_frrbcs_m_t23_i ;

for TRYPHAENA t_frrbcs_m_t23_i

Summary of main studies

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Summary of efficacy for the NEOSPHERE

Title: A randomized, multicenter, multinational Phase II study on trastuzumab plus docetaxel versus trastuzumab plus docetaxel plus pertuzumab versus trastuzumab plus pertuzumab versus pertuzumab and docetaxel in patients with locally advanced, inflammatory or early stage HER2 positive breast cancer.	
Study identifier	**NEOSPHERE (WO20697)**

Design	Phase II, randomized, double-blind, placebo-controlled, international, multicenter clinical trial		
	Duration of main phase:		17 Dec 2007–12 July 2013
Hypothesis	Superiority		
Treatments groups (417 patients in total)	Arm A (T + D)		• Trastuzumab: loading dose of 8 mg/kg IV, followed by 6 mg/kg IV q3w; • Docetaxel: dose of 75 mg/m^2 escalating to 100mg/m^2 IV q3w. 107 randomized patients
	Arm B (Ptz + T + D)		• Pertuzumab: loading dose of 840 mg IV, followed by 420 mg IV q3w; • Trastuzumab: loading dose of 8 mg/kg IV, followed by 6 mg/kg IV q3w; • Docetaxel: dose of 75 mg/m^2 escalating to 100 mg/m^2 IV q3w. 107 randomized patients
	Arm C (Ptz + T)		• Pertuzumab: loading dose of 840 mg IV, followed by 420 mg IV q3w; • Trastuzumab: loading dose of 8 mg/kg IV, followed by 6 mg/kg IV q3w. 107 randomized patients
	Arm D (Ptz + D)		• Pertuzumab: loading dose of 840 mg IV, followed by 420 mg IV q3w; • Docetaxel: dose of 75 mg/m^2 escalating to 100 mg/m^2 IV q3w. 96 randomized patients
Endpoints and definitions	Primary endpoint	**bpCR (ypT0/is)**	**bpCR:** pathological Complete Response; **ypT0/i**s: TNM Staging System; **Description:** Eradication of all invasive tumor from the breast; in situ disease might remain); nodal status not considered.
	Exploratory endpoint(s)	**tpCR (ypT0/is ypN0)**	**tpCR:** total pathological Complete Response; **ypT0/is ypN0**: TNM Staging System; **Description:** Eradication of all invasive tumor from the breast; in situ disease might remain; node negative at definitive surgery.
		GBG pCR (ypT0 ypN0)	**GBG pCR:** German Breast Group pathological Complete Response; **ypT0 ypN0:** TNM Staging System; **Description:** Eradication of all invasive and non-invasive tumor from the breast; no remaining in situ disease; node negative at definitive surgery.
	Secondary endpoint	**Clinical Response Rate**	Best clinical Response (BCR) was defined as complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD), and clinical response rate was defined as the proportion of patients who achieved a clinical response (CR or PR) at any time pre-surgery. Clinical response was required to be assessed by clinical breast examination (CBE) and identified as per local practice based on RECIST criteria.
		Time to Clinical Response	Time from the date of first dose received to the date of assessment of clinical response.

		Breast Conserving Surgery (BCS)	Proportion of patients who achieved BCS out of the ITT population without inflammatory breast cancer, as these patients received mastectomy irrespective of their response to neo-adjuvant treatment.
Database lock	22 December 2009		

Results and Analysis

Analysis description	**Primary Analysis**				
Analysis population and time point description	Intent to treat population (ITT) N=417				
Descriptive statistics and estimate variability	Treatment group		T+D (Arm A)	Ptz+T+D (Arm B)	Ptz+T (Arm C)	Ptz+D (Arm D)
	Number of subject		107	107	107	96
	bpCR, ypT0/is (%) [95% CI]		31 (29.0%) [20.6;38.5]	49 (45.8%) [36.1;55.7]	18 (16.8%) [10.3;25.3]	23 (24.0%) [15.8;33.7]
	tpCR, ypT0/is ypN0 (%) [95% CI]		23 (21.5%) [14.1;30.5]	42 (39.3%) [30.0;49.2]	12 (11.2%) [5.9; 18.8]	17 (17.7%) [10.7;26.8]
	GBG pCR, **ypT0 ypN0** (%) [95% CI]		13 (12.1%) [6.6; 19.9]	35 (32.7%) [24.0;42.5]	6 (5.6%) [2.1; 11.8]	13 (13.5%) [7.4; 22.0]
	Overall clinical response (CR + PR) rate		79 (81.4%)	88 (88.0%)	65 (66.3%)	65 (73.9%)
	Best clinical response (%)	**CR**	21 (21.6%)	25 (25.0%)	11 (11.2%)	14 (15.9%)
		PR	58 (59.8%)	63 (63.0%)	54 (55.1%)	51 (58.0%)
		SD	17 (17.5%)	12 (12.0%)	31 (31.6%)	23 (26.1%)
		PD	1 (1.0%)	0	2 (2.0%)	0
	Time to Clinical response Weeks (N) [80% CI]		6.3 (99) [6;7]	6.3 (101) [4; 7]	6.9 (102) [6; 9]	7.3 (91) [6; 9]
	Breast conserving surgery (%), [N]		14 (22.6%) [62]	13 (23.2%) [56]	11 (18.0%) [61]	19 (31.7%) [60]
Effect estimate per comparison	Primary endpoint – bpCR, ypT0/is		Comparison groups	Three individual hypotheses were tested: [Arm A (T+D) vs. Arm B (Ptz+T+D)]; [Arm A (T+D) vs. Arm C (Ptz+T)]; [Arm D (Ptz+D) vs. Arm B (Ptz+T+D)]. bpCR rate: 25% for Arm A (T+D) and Arm D (Ptz+D); 40% for Arm B (Ptz+T+D) or Arm C (Ptz+T).		
			Cochrane-Mantel-Haenszel (CMH) test			
			p-value from CMH	0.0094 (vs. T+D) 0.0198 (vs. T+D) 0.0010 (vs. Ptz+T+D)		
			P-value (with Simes corr. for CMH test)	0.0141 (vs. T+D) 0.0198 (vs. T+D) 0.0030 (vs. Ptz+T+D)		
Notes	-					

Summary of efficacy for the TRYPHAENA study

Title: A randomized, multicentre, multinational Phase II study to evaluate pertuzumab in combination with trastuzumab, given either concomitantly or sequentially with standard anthracycline-based chemotherapy or concomitantly with a non-anthracycline-based chemotherapy regimen, as neoadjuvant therapy for patients with locally advanced, inflammatory or early stage HER2-positive breast cancer.			
Study identifier	BO22280		
Design	Randomised, multicenter, multinational, open-label		
	Duration :		26 Nov 09 – 22 July13 (3rd clinical cutoff)
Hypothesis	Exploratory: The aim of this study was to explore and make a preliminary assessment of the tolerability of neoadjuvant treatment with the combination of pertuzumab and trastuzumab when given with either anthracycline or non-anthracycline based chemotherapy.		
Treatments groups	Arm A		5-Fluorouracil, epirubicin with cyclophosphamide (FEC), trastuzumab and pertuzumab every three weeks for three cycles, followed by docetaxel, trastuzumab and pertuzumab every three weeks, for three cycles.
	Arm B		FEC every three weeks for three cycles, followed by docetaxel, trastuzumab and pertuzumab every three weeks, for three cycles.
	Arm C		Trastuzumab, carboplatin, docetaxel (TCH) and pertuzumab every three weeks, for six cycles.
Endpoints and definitions	Co-Primary endpoint	LVSD	Incidence of symptomatic cardiac events as assessed by the investigator
	Co-primary endpoint	LVEF	Clinically significant decline in left ventricular ejection fraction over the course of the neoadjuvant period (LVEF decline ≥ 10% from baseline and to a value below 50%.
	Secondary endpoint	pCR	Pathologic complete response
	Secondary endpoint		Clinical response rate (Overall response (CR+PR) based on clinical breast examination)
	Secondary endpoint		Time to clinical response
	Secondary endpoint	BCS	Breast conserving surgery rate. Rate of planned mastectomies that underwent BCS.
	Secondary endpoint	OS	Overall survival
	Secondary endpoint	PFS	Progression-free survival
	Secondary endpoint	DFS	Disease-free survival
	Secondary endpoint		Incidence of symptomatic cardiac events and asymptomatic LVEF events
	Secondary endpoint		LVEF measures over the course of the study

	Secondary endpoint		Incidence and severity of AEs and SAEs
	Secondary endpoint		Laboratory test abnormalities.
	Explorative endpoint		Evaluation of biomarkers
Database lock	21 June 2011		

Results and Analysis

Analysis description	**Second update**		
Analysis population and time point description	Intent to treat		
Descriptive statistics and estimate variability	Treatment group	Ptz+T+FEC/Ptz+T+D (Arm A)	FEC/Ptz+T+D (Arm B)	Ptz+TCH (Arm C)
	Number of subject	72	75	76
	LVSD	0	2 (2.7%)	1 (1.3%)
	LVEF	5 (6.6%)	12 (16.0%)	8 (10.5%)
	pCR (ypT0/is)	45 (61.9%)	43 (57.3%)	51 (66.2%)
	95% CI	49.5; 72.8	45.4; 68.7	54.6; 76.6
	Clinical response rate	67 (91.8%)	71 (94.7%)	69 (89.6%)
	Time to clinical response (median, weeks) 80% CI	3.6 3-18	6.3 3-20	4.9 3-18
	BCS rate	10 (21.7%)	6 (16.7%)	10 (27%)
Effect estimate per comparison	No formal hypothesis testing was planned.		

Clinical studies in special populations

Efficacy analyses for the following patient subgroups were performed for both studies and are presented above: Age group ≥65 years, Age group ≥75 years, Race (White, Black, Asian, Other), Region (Europe, Asia, North America, South America and Other).

2.4.3. Supportive study

A summary of efficacy data from the CLEOPATRA study, which was the pivotal trial for the approval of pertuzumab in the treatment of metastatic breast cancer (MBC), was included in present application.

In metastatic breast cancer, the approval was based on a multicentre, randomized, double-blind, placebo-controlled trial (CLEOPATRA) in 808 patients with HER2-positive MBC. Patients were randomly allocated (1:1) to receive pertuzumab in combination with trastuzumab and docetaxel or placebo in combination with trastuzumab and docetaxel.

The improvement in progression-free survival (PFS) in the pertuzumab arm was statistically significant [HR, 0.62; 95% confidence interval (CI), 0.51–0.75; p< 0.0001, log-rank test]. Moreover, a statistically significant improvement in OS of 15.7 months was observed with a HR of 0.68 (95% CI, 0.56-0.84; p=0.0002). The median OS was 56.5 months in the pertuzumab+trastuzumab+docetaxel arm versus 40.8 months in the placebo+trastuzumab+docetaxel arm.

2.4.4. Discussion on clinical efficacy

Design and conduct of clinical studies

The MAH provided data from two open-label phase II studies (studies NEOSPHERE and TRYPHAENA), randomised and multi-centre. Both studies had similar patient populations, but differed slightly with regard to treatment regimens and main objectives. Nonetheless, several of the endpoints were identical.

The inclusion and exclusion criteria define the target population as female patients >18 years with early breast cancer that are HER2-postive (HER2+), where the primary tumour is > 2 cm with no metastasis. The study population is considered to reflect future patients that could benefit from pertuzumab in the neoadjuvant setting and the MAH has adequately reflected the inclusion/exclusion criteria in the SmPC (see SmPC section 5.1).

The choice of treatments and doses reflect current clinical practice and are as such acceptable. With regards to the NEOSPHERE study, it is however noted that the treatment regimens included Fluorouracil, epirubicin and cyclophosphamide (FEC) in the adjuvant regimens only. The neoadjuvant regiments consisted in HER2-therapy (trastuzumab and/or pertuzumab) in combination with a taxane (docetaxel). In operable cases, the timing of treatment (pre- versus post-operative) has no effect on long-term outcomes (Mieog et al, 2007). Due to the well-known cardiotoxicity of trastuzumab, it is not be administrated concomitantly with anthracyclines (see SmPC trastuzumab (Herceptin)), while the combination of trastuzumab and a taxane is safer in terms of cardiotoxicity (Senkus et al. Annals of Oncology, 2013). However, in order to increase the chances of pCR, the CHMP noted that it would have been preferable to add, e.g. FEC or TCH in the neoadjuvant setting in the NEOSPHERE study. The MAH argued that the study was designed so FEC chemotherapy was given after surgery in order to isolate the effect of pertuzumab in the neoadjuvant setting which is a reasonable argument.

The results from the TRYPHAENA study showed that the pCR rates were higher (compared with the NEOSPHERE study) and comparable across all three treatment arms. However, there was no control arm in the TRYPHAENA study, which was designed with safety measures as primary objective and efficacy measures as secondary objectives. One would expect higher pCR rates if the anthracycline component of the NEOSPHERE regimen was brought forward, and there is no scientific reason to expect that the additional benefit of pertuzumab would be lost, if FEC was given in the neoadjuvant setting. Overall, and also taking into consideration the solid evidence from the CLEOPATRA study (see

section on supportive data) and the expected confirmatory results from the APHINITY study (see further below), the design of the NEOSPHERE study is considered acceptable from a scientific point of view to support the applied extension of indication.

The MAH was also requested to compare and discuss the TRYPHAENA study with similar neoadjuvant trials published in the literature. Despite the limitations of cross-trial comparison, it was observed that the tpCR rates are consistently higher in the TRYPHAENA study. Thus, there is no reason to suspect that the addition of FEC in the neoadjuvant setting would dilute the effect of pertuzumab, or in other words, there seems to be an added benefit of combining FEC+trastuzumab and pertuzumab in the neoadjuvant setting.

Docetaxel dose escalation was not permitted in Arm C of study TRYPHAENA, consistent with standard practice for the TCH regimen. The rationale is endorsed. When administered with Perjeta the recommended initial dose of docetaxel is 75 mg/m^2, administered thereafter on a 3 weekly schedule. The docetaxel dose should not be escalated when used in combination with carboplatin, trastuzumab and Perjeta (see SmPC section 4.2).

The pCR was defined as ypT0/is and the MAH has also provided results based on the different definitions of pCR. To fulfil the definition of tpCR (ypT0/is ypN0) as referred to in the *Draft Guidance on The role of the pathological Complete Response as an 4 endpoint in neoadjuvant breast cancer studies* (EMA/CHMP/151853/2014) adequate data on staging and management of axillary lymph nodes would be needed. In both NEOSPHERE and TRYPHAENA studies, sentinel node biopsy at study entry was not prospectively collected. However, 5 and 10 patients were identified by the MAH. Of the 5 patients enrolled in NEOSPHERE, 2 were sentinel lymph node (SLN)-positive and 3 SLN-negative, none was enrolled in the D+T+Ptz arm. In the TRYPHAENA, the number of retrieved sentinel node biopsies was 10 of whom 5 achieved a bpCR and tpCR. None had any further axillary sampling or axillary surgery reported and the axillary nodal status at primary surgery was based on baseline SLN biopsy result. Hence, the low number of patients for whom the SLN status is available together with the lack of further axillary evaluation did not allow any conclusion on the potential impact of nodal status on bp/tpCR.

The Applicant has used dynamic allocation in the NEOSPHERE study due to the likelihood of small strata. Although less preferred since such deterministic schemes should be avoided as discussed in the CHMP guideline (EMA/295050/2013), it was considered acceptable. To support the dynamic allocation, the p-values were supplemented with randomisation test that supported the primary analysis.

Both studies were open-label. Blinded review of the specimens and central review of pathology slides was requested but not provided as many sites are now closed since the NEOSPHERE study is complete and the TRYPHAENA study has been running for several years. Nevertheless, efficacy outcomes (PFS and DFS) at 5 years in the NEOSPHERE showed HRs in favour of Arm B (pertuzumab containing arm). Although the NEOSPHERE study was not designed to detect a difference in terms of PFS/DFS/OS between the different treatment arms, it is still encouraging to see these results in favour of the pertuzumab arm. Also, recent data from the GEPAR-SEPTO trial (comparison of two forms of paclitaxel) support the findings in the TRYPHAENA study (Untch M et al., Abstract S2-07, 2014 San Antonio Breast Cancer Symposium). Thus, the likelihood of biased reviews of pathology slides/specimens in the NEOSPHERE and TRYPHAENA studies is considered to be very low.

The MAH noted that in general the pathologists were not informed of patients' treatment allocation. According to the results of a survey performed by the MAH, pathologists were only aware of treatment arm in 4.6% (19 patients) in NEOSPHERE and 9.8% (22 patients) in TRYPHAENA. Thus, assuming that these results were all biased, it would still not change the overall results. Furthermore, an analysis of

pCR status by region shows that pCR trends in the different regions are consistent with the overall results.

The Applicant claimed that studies NEOSPHERE and TRYPHAENA were conducted in accordance with the principles of GCP. Several inspections were conducted by other national competent authorities. Only one inspection found critical and major issues in one centre participating in the TRYPHAENA study. These findings are not considered to have an impact on the overall benefit-risk balance of pertuzumab.

Efficacy data and additional analyses

There was a clear and statistically significant difference in bpCR of 16.8% in favour of the Ptz+T+D arm in NEOSPHERE study, where a bpCR rate of 45.8% was achieved, compared to 29% in the T+D. Ptz+T and Ptz+D had lower bpCR rates compared to T+D. The tpCR (ypT0/is N0) rates showed the same pattern with a 17.8% difference in favour of the Ptz+T+D arm compared to the Ptz+T arm.

Regardless of treatment arm, the pCR rates achieved in the TRYPHAENA study were consistently high and similar across all treatment groups. In general, the pCR rates were higher compared to the Ptz+T+D arm in the NEOSPHERE study. The higher rate of pCR in the TRYPHAENA study reflects the higher number cycles of treatment in the neoadjuvant setting, and the use of the combination of pertuzumab, trastuzumab and chemotherapy in all 3 treatment arms.

Clinical responses were evaluated differently in the two studies. In the NEOSPHERE it was based on clinical breast examination (CBE) and imaging, while in the TRYPHAENA study it was only based on CBE. Hence, cross-comparison of data may only be partially justified. There were high and similar overall response (CR+PR) rates in the Ptz+T+D arm in the NEOSPHERE study and in all three arms of the TRYPHAENA study. Time to clinical response was around 6-7 weeks in all arms in the NEOSPHERE study. In the TRYPHAENA study, time to clinical response was 3.6 weeks in Arm A compared to 6.3 weeks and 4.9 weeks in Arm B and C respectively.

The number of planned mastectomies that underwent breast conserving surgery (BCS) was highest (31.7%) in the Ptz+D arm in the NEOSPHERE study. However, this group of patients did not achieve the highest pCR rate. The BCS rates were similar between the three treatment arms in the TRYPHAENA study and comparable with the T+D and Ptz+T+D arms in the NEOSPHERE study. The NEOSPHERE and TRYPHAENA studies were not designed to show a difference in BCS and the reasons for choosing mastectomy or BCS were not collected. Thus, despite the higher pCR rate in arm T+D and Ptz+T+D, no firm conclusions can be drawn on the BCS.

There were very few patients over 65 years in the submitted studies. Limited data are available on the safety and efficacy of Perjeta in patients ≥ 65 years of age (see SmPC section 4.2).

Pertuzumab has not been investigated in a paediatric patient population or in patients with hepatic impairment (see SmPC section 4.2).

The enrolled population was overall representative of the target patient population in both studies. However, a high percentage of tumours in both studies were classified unknown as histological grade (35% in NEOSPHERE and 20.4% in TRYPHAENA). There are no obvious reasons for “unknown grade” in this group of patients, but it seems to be site-specific and not by geographic region. Furthermore, tumour grade is not required for treatment decision. However, recent publications show a clear link between pCR rates in low-grade vs. high-grade disease. A meta-analysis of neoadjuvant studies has shown that pCR rates were lower in patients with low-grade, hormone receptor-positive (HR+) tumours, and higher in the following tumour subtypes in increasing order: high-grade HR+, HR+/HER2+, triple negative, and hormone receptor-negative (HR–)/HER2+. In addition, patients with

more aggressive tumour subtypes who achieved pCR seemed to have greater EFS benefit compared to patients who did not achieve pCR (Cortazar et al., Lancet 2014). An analysis of pCR, excluding patients with tumours of "unknown grade" showed that bpCR and tpCR were comparable with the findings in the ITT analysis (data not shown) which is reassuring. Thus, it seems that the overall estimate is not influenced by the population of patients with "unknown tumour grade".

tpCR is, as expected highest in the ptz+T+D arm in the NEOSPHERE study and comparable between Arms A-C in the TRYPHAENA study with regard to patients with high-grade disease (poorly differentiated). Very few patients had low grade disease (well differentiated), and a meaningful comparison is not possible.

A comparison of high-grade HR+ disease with HR+ in general showed higher rate of tpCR in the Ptz+T+D arm in the NEOSPHERE study. This is in line with the findings in the meta-analysis by Cortazar et al, Lancet 2014. The same comparison in the TRYPHAENA study showed comparable effect in both groups. However, the subgroups are small and no firm conclusions can be drawn.

In the overall patient population of both studies, efficacy results are considered clinically relevant.

In both studies pCR rates and magnitude of improvement with pertuzumab were lower in the subgroup of patients with hormone-receptor-positive tumours compared to patients with hormone receptor-negative tumours. In particular, in NEOSPHERE (study including non pertuzumab-containing control arm) subgroup analyses, patients with hormone receptor-positive disease had lower bpCR rates (5.9% - 26%, across treatment arms [highest in Ptz+T+D arm]) than patients with hormone receptor-negative disease (27.3% - 63.2%, across treatment arms [highest in Ptz+T+D arm]).

The poor response in HR-positive disease in NEOSPHERE and TRYPHAENA studies is biologically plausible and consistent with the majority of data reported in the literature. However, the importance of HER2-targeted therapy in HR+ disease should not be neglected and hormone therapy alone has shown very low efficacy in patients with HR+/HER2+ disease in a number of trials (TAnDEM (Kaufman B et al. 2009, J Clin Oncol.); study eLEcTRA (Huober J, et al. 2009, Cancer Res.), study CALGB-40302 (Burstein HJ et al. 2014, J Clin Oncol). In addition, the published meta-analyses driven by the FDA (Cortazar et al. 2014, Lancet), which included individual patient data from approximately 12.000 patients, showed that there is a clear advantage in terms of long-term outcomes in patients with HER2+ disease, who achieve a pCR, irrespective of hormone receptor (HR) status. Moreover, the CLEOPATRA study clearly showed a Hazard Ratio for OS of 0.71 (0.51, 0.96) in patients with HR+ disease, compared with 0.61 (0.47, 0.81) in patients with HR-negative disease. Thus, the CHMP concluded that there is solid evidence for a statistically significant and clinically relevant effect of pertuzumab in HER2+ breast cancer in the metastatic setting, regardless of hormone receptor status. In the context of the totality of data and the above discussion, it is reasonable to expect that this should also be the case in the neoadjuvant setting.

Regarding pCR data by disease stage/type, tpCR by disease stage/type seems to in line with the overall estimate. In both studies, pCR rates were similar in patients with operable versus locally advanced disease (see SmPC section 5.1). Regarding the tumour stage it is noted that a low percentage of IBC was included. However, baseline demographic and disease characteristics were sufficiently consistent with expectations for such a population. In the NEOSPHERE study, there were too few patients with inflammatory breast cancer to draw any firm conclusions, but the pCR rate was higher in patients who received Perjeta plus trastuzumab and docetaxel. In the TRYPHAENA study, there were also too few patients with inflammatory breast cancer to draw any firm conclusions. This has been reflected in the SmPC (see SmPC section 5.1).

The DFS, PFS and OS data are not mature yet for the TRYPHAENA study. DFS and PFS data were provided for the NEOSPHERE study. The long term outcome data (PSF, DFS, PFS pCR versus non-pCR) in the overall population of the NEOSPHERE study, although not statistically powered and with wide CIs, showed HRs consistent with the observed pCR increase. However, none of the two studies (NEOSPHERE and TRYPHAENA) were powered to detect a difference. Efficacy data that should permit confirmation of the positive results seen in the NEOSPHERE and TRYPHAENA studies are expected from the much larger phase III study (APHINITY) of adjuvant trastuzumab and chemotherapy plus pertuzumab or placebo in patients with primary operable breast cancer.

The SAG Oncology was consulted and discussed whether the difference in tpCR rate of 17.8% between Arm A and B in the NEOSPHERE study is sufficiently large enough to translate into a significant difference with regard to DFS and OS. Given the existing uncertainty about pCR as a surrogate for DFS and OS, the SAG concluded that a difference of 18% does not allow to automatically conclude a significant difference with regard to long-term benefit. In addition NEOSPHERE design was not optimal to address this question of surrogacy (not all major treatments were given in the neoadjuvant setting, e.g., anthracyclines, and this may lead to overestimating the treatment effect of the experimental drug pertuzumab). However, the SAG agreed that in the context of the totality of the data, in particular, the strong biological rationale for the combination, the compelling efficacy results in the metastatic setting, the acceptable toxicity profile (see clinical safety), and the observed effect in terms of pCR, it is reasonably likely that neoadjuvant treatment with pertuzumab is associated with a benefit in terms of DFS and OS. A precise estimation of the expected long-term benefit is currently not possible based on the available data. Although based on a small number of events (18% and 16% for the control and pertuzumab group, respectively, cut-off 20 October 2014), exploration of the event-free survival by treatment showed a HR of 0.69 (95% CI [0.34, 1.40]), which is encouraging.

Importantly, the trial in the adjuvant setting (APHINITY) has completed its recruitment. The final analysis of invasive disease-free survival (IDFS) from the APHINITY study (phase III) should permit confirmation of the clinical benefit of pertuzumab observed in the neoadjuvant setting from the NEOSPHERE and TRYPHAENA studies (see Annex II).

The MAH has also initiated the BERENICE study, which will enrol a similar patient population to that enrolled in the NEOSPHERE and TRYPHAENA studies. The primary endpoint of the study is cardiac safety of pertuzumab in combination with two commonly used neoadjuvant regimens. Secondary endpoints include overall safety and pCR rate. The study is planned to enrol approximately 400 patients (200 patients in each cohort). Safety and efficacy data from the neoadjuvant period are anticipated in 2017. Thus, this study will also provide valuable information with regard to efficacy and safety on the use of pertuzumab in the neoadjuvant setting (see Annex II).

The SAG Oncology also discussed the data in the HR-positive population and noted that the lower pCR rates observed in patients with HR+ tumours adds to the uncertainty with regard to long-term benefit. However, the subgroup analysis is based on very limited data and it is difficult to rule out the play of chance. Although the observed effect was lower in patients with HR+ tumours, in the context of the totality of the data (see above), the effect is still considered to be reasonably likely associated with a benefit in terms of long-term outcomes. Further understanding about the long-term effects in this subgroup of patients is expected on the basis of the ongoing adjuvant trial (APHINITY).

2.4.5. Conclusions on clinical efficacy

In conclusion, in the context of the totality of the data, in particular, the strong biological rationale for the combination, the compelling efficacy results in the metastatic setting, the acceptable toxicity

profile, and the observed effect in terms of pCR, the efficacy is considered established. Although not statistically significant, efficacy outcome data (DFS and OS) from the NEOSPHERE study shows a trend in favour of pertuzumab. This should also be seen in light of the survival benefit of adding pertuzumab to trastuzumab in the metastatic setting.

Confirmatory study data in terms of DFS and OS are considered necessary to address long term efficacy of pertuzumab in the neoadjuvant setting. Study APHINITY has been included as a condition in the Annex II as post-authorisation efficacy study (PAES). Further efficacy data are also expected from the post-authorisation safety study BERENICE.

Post-authorisation efficacy study (PAES): In order to provide long-term efficacy data in terms of DFS and OS, the MAH should submit the results of study BO25126 (APHINITY), a randomized multicenter, double-blind, placebo-controlled comparison of chemotherapy plus trastuzumab plus placebo versus chemotherapy plus trastuzumab plus pertuzumab as adjuvant therapy in patients with operable HER2-positive primary breast cancer	May 2017
Post-authorisation safety study (PASS): In order to evaluate cardiac safety and provide further efficacy data in the neoadjuvant setting, the MAH should submit the results of study WO29217 (BERENICE), a multicentre, multinational, Phase II study to evaluate pertuzumab in combination with trastuzumab and standard neoadjuvant anthracycline-based chemotherapy in patients with HER2-positive, locally advanced, inflammatory, or early-stage breast cancer.	May 2017

2.5. Clinical safety

2.5.1. Introduction

The evaluation of clinical safety included safety data from the two neoadjuvant studies, NEOSPHERE (WO20697) and TRYPHAENA (BO22280), and a supporting study, CLEOPATRA (WO20698/TOC4129g) in patients with metastatic breast cancer.

Overall, the two neoadjuvant studies provided safety data for 532 patients treated with pertuzumab in combination with trastuzumab and chemotherapy (e.g., docetaxel, FEC or TCH) in the neoadjuvant setting. This included safety data from 309 patients in the NEOSPHERE study and 223 patients in the TRYPHAENA study.

The supporting study CLEOPATRA provided safety data from 408 patients with metastatic breast cancer, who were exposed to pertuzumab in combination with trastuzumab and docetaxel, i.e., the same regimen used during the neoadjuvant phase in the Ptz+T+D arm of the NEOSPHERE study and part of the neoadjuvant regimen used in two of the treatment arms in the TRYPHAENA study (Ptz+T+FEC/Ptz+T+D and FEC/Ptz+T+D).

As NEOSPHERE, TRYPHAENA and CLEOPATRA evaluated different combination regimens in different patient populations (LABC/IBC/EBC vs. metastatic breast cancer), safety data from the three trials were presented as stand-alone tables.

2.5.2. Patient exposure

Table 30: Summary of total dose of pertuzumab received in NEOSPHERE

Protocol: WO20697
Analysis: Safety (By Treatment Received)
Snapshot Date: 22FEB2010 Clinical Cut-Off Date: 22DEC2009

	Trastuzumab + Pertuzumab + Docetaxel (N=107)	Trastuzumab + Pertuzumab (N=108)	Pertuzumab + Docetaxel (N=94)
No of cycles administered per patient			
n	107	108	94
Mean	3.9	3.9	3.9
SD	0.47	0.42	0.48
Median	4.0	4.0	4.0
Range	1-4	2-4	1-4
Total Dose Received (mg)			
n	107	108	94
Mean	2059.6	2047.7	2051.0
SD	280.79	177.57	202.74
Median	2100.0	2100.0	2100.0
Range	300-2940	1260-2100	840-2100
No (%) of patients completing at least			
1 Cycle	107 (100%)	108 (100%)	94 (100%)
2 Cycles	105 (98%)	108 (100%)	93 (99%)
3 Cycles	104 (97%)	104 (96%)	90 (96%)
4 Cycles	102 (95%)	100 (93%)	88 (94%)

Program : $PROD/cdpl1450/wo20697/t_umedtl.sas
Output : $PROD/cdpl1450/i20697g/reports/t_umedtl_per_neoa_ssp_s.out
12MAR2010 15:11
Source: t_umedtl_per_neoa_ssp_s from NEOSPHERE primary CSR

Table 31: Summary of total dose of pertuzumab received in TRYPHAENA

Protocol: BO22280
Analysis: Safety (By Treatment Received)
Snapshot Date: 01SEP2011 Clinical Cut-Off Date: 21JUN2011

	FEC+P+T x3/ DOC+P+T x3 (N=72)	FEC x3/ DOC+P+T x3 (N=75)	TCH+P x6 (N=76)
No of cycles administered per patient			
n	72	70	76
Mean	5.8	2.9	5.7
SD	0.78	0.42	1.02
Median	6.0	3.0	6.0
Range	1-6	1-3	1-6
Total Dose Received (mg)			
n	72	70	76
Mean	2875.8	1637.8	2823.9
SD	328.07	177.29	458.03
Median	2940.0	1680.0	2940.0
Range	840-3360	840-1680	420-2940
Average Dose Received per Cycle (mg)			
n	72	70	76
Mean	499.9	572.9	497.7
SD	48.75	57.53	46.54
Median	490.0	560.0	490.0
Range	490-840	556-840	420-840
No (%) of patients completing at least			
1 Cycle	72 (100.0 %)	70 (93.3 %)	76 (100.0 %)
2 Cycles	71 (98.6 %)	67 (89.3 %)	74 (97.4 %)
3 Cycles	70 (97.2 %)	66 (88.0 %)	72 (94.7 %)
4 Cycles	70 (97.2 %)	0 (0.0 %)	72 (94.7 %)
5 Cycles	70 (97.2 %)	0 (0.0 %)	72 (94.7 %)
6 Cycles	66 (91.7 %)	0 (0.0 %)	70 (92.1 %)

Program : $PROD/cdpl1450/bo22280/t_umedtl.sas / Output : $PROD/cdpl1450/j22280a/reports/
t_umedtl_neoa_per_s.out
02SEP2011 20:14
Source : t_umedtl_neoa_per_s from TRYPHAENA primary CSR

In the CLEOPATRA study, patients received placebo+T+D or Ptz+T+D every three weeks until progression of disease, withdrawal or unacceptable toxicity. Patients were exposed to pertuzumab for a much longer time compared with patients in the NEOSPHERE and TRYPHAENA studies. On average, 25.4 cycles of Ptz+T+D have been administrated. Patients received a median of 8 cycles of Ptz+T+D. Because Ptz+T could be given after discontinuation of docetaxel, they also received a median 24 cycles of Ptz+T, including the cycles given with docetaxel. Some patients received up to 42 cycles of all three agents (Ptz+T+D).

2.5.3. Adverse events

Overview of adverse events

Table 32: Overview of adverse events during the overall treatment period in NEOSPHERE

Snapshot Date: 13AUG2012 Clinical Cut-Off Date: 09MAR2012

	Trastuzumab + Docetaxel (N=107)	Trastuzumab + Pertuzumab + Docetaxel (N=107)	Trastuzumab + Pertuzumab (N=108)	Pertuzumab + Docetaxel (N=94)	Total (N=416)
Number of patients with AEs					
Any AE	107 (100.0%)	105 (98.1%)	103 (95.4%)	94 (100.0%)	409 (98.3%)
NCI-CTCAE Grade >= 3	87 (81.3%)	78 (72.9%)	65 (60.2%)	74 (78.7%)	304 (73.1%)
Related	106 (99.1%)	105 (98.1%)	99 (91.7%)	93 (98.9%)	403 (96.9%)
Serious AE	21 (19.6%)	22 (20.6%)	19 (17.6%)	21 (22.3%)	83 (20.0%)
AE Leading to Discontinuation of study medication	0 (0.0%)	5 (4.7%)	8 (7.4%)	4 (4.3%)	17 (4.1%)
AE Leading to Dose Interruption/Modification	54 (50.5%)	55 (51.4%)	48 (44.4%)	54 (57.4%)	211 (50.7%)
AE Resulting in Death	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
AE During Pertuzumab infusion	0 (0.0%)	8 (7.5%)	14 (13.0%)	1 (1.1%)	23 (5.5%)
NCI-CTCAE grade >= 3	0 (0.0%)	1 (0.9%)	2 (1.9%)	0 (0.0%)	3 (0.7%)
Number of patients with AEs of Special Interest*					
Symptomatic LVSD assessed by the Investigator	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
NYHA class III/IV	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Left Ventricular Dysfunction [1]	2 (1.9%)	8 (7.5%)	0 (0.0%)	5 (5.3%)	15 (3.6%)
NCI-CTCAE grade >= 3	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
SAEs Suggestive of CHF [2]	0 (0.0%)	3 (2.8%)	1 (0.9%)	0 (0.0%)	4 (1.0%)
NCI-CTCAE grade >= 3	0 (0.0%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	2 (0.5%)
Diarrhoea [3]	41 (38.3%)	55 (51.4%)	46 (42.6%)	53 (56.4%)	195 (46.9%)
NCI-CTCAE grade >= 3	4 (3.7%)	7 (6.5%)	3 (2.8%)	5 (5.3%)	19 (4.6%)
Rash[2]	38 (35.5%)	48 (44.9%)	36 (33.3%)	42 (44.7%)	164 (39.4%)
NCI-CTCAE grade >= 3	3 (2.8%)	3 (2.8%)	1 (0.9%)	2 (2.1%)	9 (2.2%)
Leukopenia	88 (82.2%)	74 (69.2%)	54 (50.0%)	75 (79.8%)	291 (70.0%)
NCI-CTCAE grade >= 3	82 (76.6%)	66 (61.7%)	47 (43.5%)	66 (70.2%)	261 (62.7%)
Leukopenic Infection [4]	4 (3.7%)	3 (2.8%)	1 (0.9%)	2 (2.1%)	10 (2.4%)
NCI-CTCAE grade >= 3	4 (3.7%)	3 (2.8%)	1 (0.9%)	2 (2.1%)	10 (2.4%)
Febrile Neutropenic Infection [4]	1 (0.9%)	2 (1.9%)	0 (0.0%)	1 (1.1%)	4 (1.0%)
NCI-CTCAE grade >= 3	1 (0.9%)	2 (1.9%)	0 (0.0%)	1 (1.1%)	4 (1.0%)
Hypersensitivity/anaphylaxis [2]	2 (1.9%)	7 (6.5%)	14 (13.0%)	9 (9.6%)	32 (7.7%)
NCI-CTCAE grade >= 3	0 (0.0%)	2 (1.9%)	3 (2.8%)	0 (0.0%)	5 (1.2%)
Interstitial Lung Disease [2]	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.1%)	1 (0.2%)
NCI-CTCAE grade >= 3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
QT Prolongation [2]	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (1.1%)	2 (0.5%)
NCI-CTCAE grade >= 3	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (1.1%)	2 (0.5%)
Mucositis [2]	50 (46.7%)	58 (54.2%)	42 (38.9%)	47 (50.0%)	197 (47.4%)
NCI-CTCAE grade >= 3	0 (0.0%)	3 (2.8%)	0 (0.0%)	1 (1.1%)	4 (1.0%)
Thromboembolic Event Venous [2]	0 (0.0%)	2 (1.9%)	0 (0.0%)	2 (2.1%)	4 (1.0%)
NCI-CTCAE grade >= 3	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.1%)	1 (0.2%)

[1] Left ventricular Dysfunction AEs identified by selecting the PT "Left Ventricular Dysfunction"
[2] AEs identified using the appropriate AEGT or SMQ - see glossary L_UD09_AEGT for a more detailed description
[3] Diarrhoea AEs identified from the PT "Diarrhoea"
[4] Leukopenic Infection/febrile neutropenic infection events identified as any event in the Infections/infestations SOC with a start date <=14 days after the start date of a NCI-CTCAE Grade >=3 event in the SMQ (narrow) "Haematopoietic leukopenia"/febrile neutropenia PT respectively
* terminology has subsequently changed to 'events to monitor'
Program : $PROD/cdp11450/i206971/t_fae2.sas / Output : $PROD/cdp11450/i206971/reports/t_fae2_oval_ssp_s.out
05SEP2012 19:14
Source: t_fae2_oval_ssp_s

Table 33: Overview of adverse events during the overall treatment period in TRYPHAENA

t_fae2_oval_s Overview of Adverse Events During the Neoadjuvant and Adjuvant Period
Protocol: BO22280
Analysis: Safety (By Treatment Received)
Snapshot Date: 04JUL2012 Clinical Cut-Off Date: 04JUL2012

	TOTAL (N=223)	FEC+P+T x3/ DOC+P+T x3 (N=72)	FEC x3/ DOC+P+T x3 (N=75)	TCH+P x6 (N=76)
Number of patients with AEs				
Any AE	222 (99.6%)	72 (100.0%)	74 (98.7%)	76 (100.0%)
NCI-CTCAE Grade >= 3	155 (69.5%)	53 (73.6%)	46 (61.3%)	56 (73.7%)
Related	220 (98.7%)	72 (100.0%)	72 (96.0%)	76 (100.0%)
Serious AE	72 (32.3%)	23 (31.9%)	18 (24.0%)	31 (40.8%)
AE Leading to Discontinuation of study medication	20 (9.0%)	7 (9.7%)	7 (9.3%)	6 (7.9%)
AE Leading to Dose Interruption/Modification	96 (43.0%)	30 (41.7%)	27 (36.0%)	39 (51.3%)
AE Resulting in Death	1 (0.4%)	1 (1.4%)	0 (0.0%)	0 (0.0%)
AE During Pertuzumab infusion	11 (4.9%)	3 (4.2%)	4 (5.3%)	4 (5.3%)
NCI-CTCAE grade >= 3	1 (0.4%)	0 (0.0%)	0 (0.0%)	1 (1.3%)
Number of patients with Events to Monitor				
Symptomatic LVSD assessed by the Investigator	3 (1.3%)	0 (0.0%)	2 (2.7%)	1 (1.3%)
NYHA class III/IV	1 (0.4%)	0 (0.0%)	1 (1.3%)	0 (0.0%)
Left Ventricular Dysfunction [1]	18 (8.1%)	6 (8.3%)	7 (9.3%)	5 (6.6%)
NCI-CTCAE grade >= 3	3 (1.3%)	0 (0.0%)	2 (2.7%)	1 (1.3%)
SAEs Suggestive of CHF [2]	4 (1.8%)	1 (1.4%)	2 (2.7%)	1 (1.3%)
NCI-CTCAE grade >= 3	3 (1.3%)	0 (0.0%)	2 (2.7%)	1 (1.3%)
Diarrhoea [4]	148 (66.4%)	46 (63.9%)	47 (62.7%)	55 (72.4%)
NCI-CTCAE grade >= 3	16 (7.2%)	3 (4.2%)	4 (5.3%)	9 (11.8%)
Rash[2]	81 (36.3%)	27 (37.5%)	19 (25.3%)	35 (46.1%)
NCI-CTCAE grade >= 3	4 (1.8%)	2 (2.8%)	1 (1.3%)	1 (1.3%)
Leukopenia	136 (61.0%)	46 (63.9%)	41 (54.7%)	49 (64.5%)
NCI-CTCAE grade >= 3	128 (57.4%)	43 (59.7%)	38 (50.7%)	47 (61.8%)
Leukopenic Infection [3]	7 (3.1%)	3 (4.2%)	1 (1.3%)	3 (3.9%)
NCI-CTCAE grade >= 3	7 (3.1%)	3 (4.2%)	1 (1.3%)	3 (3.9%)
Febrile Neutropenic Infection [3]	3 (1.3%)	3 (4.2%)	0 (0.0%)	0 (0.0%)
NCI-CTCAE grade >= 3	3 (1.3%)	3 (4.2%)	0 (0.0%)	0 (0.0%)
Hypersensitivity/anaphylaxis [2]	22 (9.9%)	7 (9.7%)	3 (4.0%)	12 (15.8%)
NCI-CTCAE grade >= 3	5 (2.2%)	2 (2.8%)	0 (0.0%)	3 (3.9%)
Drug Related Hepatic Dysfunction [2]	20 (9.0%)	7 (9.7%)	4 (5.3%)	9 (11.8%)
NCI-CTCAE grade >= 3	4 (1.8%)	0 (0.0%)	1 (1.3%)	3 (3.9%)
Interstitial Lung Disease [2]	2 (0.9%)	0 (0.0%)	1 (1.3%)	1 (1.3%)
NCI-CTCAE grade >= 3	1 (0.4%)	0 (0.0%)	1 (1.3%)	0 (0.0%)
QT Prolongation [2]	7 (3.1%)	1 (1.4%)	4 (5.3%)	2 (2.6%)
NCI-CTCAE grade >= 3	1 (0.4%)	0 (0.0%)	1 (1.3%)	0 (0.0%)
Thromboembolic Event Venous [2]	4 (1.8%)	2 (2.8%)	1 (1.3%)	1 (1.3%)
NCI-CTCAE grade >= 3	2 (0.9%)	1 (1.4%)	1 (1.3%)	0 (0.0%)

[1] Identified by selecting the PT 'Left Ventricular Dysfunction'
[2] Identified using the appropriate AEGT or SMQ - see L_UD09_AEGT for a more detailed description
[3] Identified as an event in the 'Infections and Infestations' SOC with a date of onset <=14 days after the start date of a NCI-CTCAE grade >=3 event in the SMQ (narrow) 'Leukopenia'/PT 'Febrile neutropenia' respectively
[4] Identified by selecting the PT 'Diarrhoea'

Program : $PROD/odp11450/bo22280/t_fae2.sas / Output : $PROD/odp11450/j22280b/reports/t_fae2_oval_s.out
23AUG2012 2:30

Table 34: Overview of adverse events in CLEOPATRA (Overall study treatment period)

t_fae2_tp_s Overview of Adverse Events During the Overall Study Treatment Period by Trial Treatment
Protocol: WO20698
Analysis: Safety (By Treatment Received)
Snapshot Date: 01JUN2012 Clinical Cut-Off Date: 14MAY2012

	Total (N=804)	Placebo + Trastuzumab + Docetaxel (N=396)	Pertuzumab + Trastuzumab + Docetaxel (N=408)
Number of Patients with AEs			
Any AE	799 (99.4%)	391 (98.7%)	408 (100.0%)
NCI-CTCAE Grade >= 3	602 (74.9%)	291 (73.5%)	311 (76.2%)
Related	778 (96.8%)	381 (96.2%)	397 (97.3%)
Serious AE	263 (32.7%)	115 (29.0%)	148 (36.3%)
AE Leading to Discontinuation of study medication	239 (29.7%)	114 (28.8%)	125 (30.6%)
AE Leading to Dose Interruption/Modification	467 (58.1%)	215 (54.3%)	252 (61.8%)
AE Resulting in Death	20 (2.5%)	12 (3.0%)	8 (2.0%)
AE During Pertuzumab Infusion	59 (7.3%)	20 (5.1%)	39 (9.6%)
NCI-CTCAE grade >= 3	3 (0.4%)	1 (0.3%)	2 (0.5%)
Number of Patients with Events to Monitor			
Symptomatic LVSD adjudicated by the CRC	8 (1.0%)	4 (1.0%)	4 (1.0%)
NYHA class III/IV	3 (0.4%)	0 (0.0%)	3 (0.7%)
Symptomatic LVSD assessed by the Investigator	12 (1.5%)	7 (1.8%)	5 (1.2%)
NYHA class III/IV	7 (0.9%)	4 (1.0%)	3 (0.7%)
Left Ventricular Dysfunction[1]	56 (7.0%)	34 (8.6%)	22 (5.4%)
NCI-CTCAE grade >= 3	18 (2.2%)	13 (3.3%)	5 (1.2%)
SAE suggestive of CHF[2]	14 (1.7%)	8 (2.0%)	6 (1.5%)
NCI-CTCAE grade >=3	12 (1.5%)	7 (1.8%)	5 (1.2%)
Diarrhoea[3]	469 (58.3%)	191 (48.2%)	278 (68.1%)
NCI-CTCAE grade >= 3	57 (7.1%)	20 (5.1%)	37 (9.1%)
Rash[2]	338 (42.0%)	144 (36.4%)	194 (47.5%)
NCI-CTCAE grade >= 3	17 (2.1%)	5 (1.3%)	12 (2.9%)
Leukopenia[2]	486 (60.4%)	231 (58.3%)	255 (62.5%)
NCI-CTCAE grade >= 3	449 (55.8%)	211 (53.3%)	238 (58.3%)
Leukopenic Infection[4]	90 (11.2%)	38 (9.6%)	52 (12.7%)
NCI-CTCAE grade >= 3	28 (3.5%)	9 (2.3%)	19 (4.7%)
Febrile neutropenic Infection[4]	17 (2.1%)	3 (0.8%)	14 (3.4%)
NCI-CTCAE grade >= 3	7 (0.9%)	1 (0.3%)	6 (1.5%)
Anaphylaxis and Hypersensitivity[2]	81 (10.1%)	36 (9.1%)	45 (11.0%)
NCI-CTCAE grade >= 3	18 (2.2%)	10 (2.5%)	8 (2.0%)
Interstitial Lung Disease[2]	16 (2.0%)	6 (1.5%)	10 (2.5%)
NCI-CTCAE grade >= 3	5 (0.6%)	2 (0.5%)	3 (0.7%)
QT Prolongation[2]	14 (1.7%)	5 (1.3%)	9 (2.2%)
NCI-CTCAE grade >= 3	5 (0.6%)	1 (0.3%)	4 (1.0%)
Mucositis[2]	353 (43.9%)	150 (37.9%)	203 (49.8%)
NCI-CTCAE grade >= 3	21 (2.6%)	8 (2.0%)	13 (3.2%)
Drug related hepatic disorder[2]	85 (10.6%)	43 (10.9%)	42 (10.3%)
NCI-CTCAE grade >= 3	12 (1.5%)	5 (1.3%)	7 (1.7%)

[1] Left ventricular Dysfunction AEs identified by selecting the PT "Left Ventricular Dysfunction"
[2] AEs identified using the appropriate AEGT or SMQ - see glossary L_UD09_AEGT for a more detailed description
[3] Diarrhoea AEs identified from the PT "Diarrhoea"
[4] Leukopenic Infection/febrile neutropenic infection events identified as any event in the Infections/infestations SOC with a start date <=14 days after the start date of a NCI-CTCAE Grade >=3 event in the SMQ (narrow) "Haematopoietic leukopenia"/febrile neutropenia PT respectively

Program : $PROD/cdp11450/wo20698/t_fae2.sas / Output : $PROD/cdp11450/j20698f/reports/t_fae2_tp_s.out
13AUG2012 0:22

Adverse Events – all grades

Study NEOSPHERE

During the neoadjuvant period, the most common SOCs affected (i.e., occurring in ≥ 25% of patients across all treatment arms) were Gastrointestinal Disorders (of which diarrhea, nausea, vomiting, and stomatitis were the most common [occurring in > 10% of patients in any arm]) and General Disorders and Administration Site Conditions (most commonly fatigue, mucosal inflammation, asthenia, pyrexia, and peripheral oedema).

In the Ptz+T+D arm, there was a higher incidence of Cardiac Disorders (11.2%, vs. 4.7%, 5.6%, and 3.2% in the T+D, Ptz+T, and Ptz+D arms, respectively). Between the T+D and Ptz+T+D arms, the incidence of AEs was comparable in most SOCs, with the exception of Gastrointestinal Disorders (more events in the Ptz+T+D arm compared with the T+D arm), Blood and Lymphatic System Disorders (more events in the T+D arm compared with the Ptz+T+D arm), and Infections and Infestations (more events in the T+D arm compared with the Ptz+T+D arm).

In the neoadjuvant period, the most frequently occurring AEs (i.e., reported in ≥ 25% of patients in any arm) were alopecia, neutropenia, diarrhoea, nausea, fatigue, rash and mucosal inflammation (see Table below).

Table 35: Summary of adverse events with an incidence rate of at least 5% in NEOSPHERE (neoadjuvant period)

Protocol(s): WO20697
Analysis: SAFETY (BY TREATMENT RECEIVED) Center: ALL CENTERS
Snapshot Date: 22FEB2010 Clinical Cut-Off Date: 22DEC2009

Adverse Event	Trastuzumab + Docetaxel N = 107 No. (%)	Trastuzumab + Pertuzumab + Docetaxel N = 107 No. (%)	Trastuzumab + Pertuzumab N = 108 No. (%)	Pertuzumab + Docetaxel N = 94 No. (%)
ALOPECIA	70 (65.4)	68 (63.6)	1 (0.9)	63 (67.0)
NEUTROPENIA	67 (62.6)	54 (50.5)	1 (0.9)	59 (62.8)
DIARRHOEA	36 (33.6)	49 (45.8)	30 (27.8)	51 (54.3)
NAUSEA	39 (36.4)	41 (38.3)	15 (13.9)	34 (36.2)
FATIGUE	29 (27.1)	28 (26.2)	13 (12.0)	24 (25.5)
RASH	23 (21.5)	28 (26.2)	12 (11.1)	27 (28.7)
MUCOSAL INFLAMMATION	23 (21.5)	28 (26.2)	3 (2.8)	24 (25.5)
MYALGIA	24 (22.4)	24 (22.4)	10 (9.3)	19 (20.2)
ASTHENIA	19 (17.8)	22 (20.6)	3 (2.8)	15 (16.0)
HEADACHE	12 (11.2)	12 (11.2)	15 (13.9)	12 (12.8)
<NO INFORMATION PROVIDED>	12 (11.2)	8 (7.5)	11 (10.2)	17 (18.1)
VOMITING	13 (12.1)	14 (13.1)	5 (4.6)	15 (16.0)
PYREXIA	11 (10.3)	18 (16.8)	9 (8.3)	8 (8.5)
LEUKOPENIA	23 (21.5)	10 (9.3)	-	12 (12.8)
STOMATITIS	8 (7.5)	19 (17.8)	5 (4.6)	9 (9.6)
DYSGEUSIA	11 (10.3)	16 (15.0)	5 (4.6)	7 (7.4)
DECREASED APPETITE	7 (6.5)	15 (14.0)	2 (1.9)	14 (14.9)
ARTHRALGIA	9 (8.4)	11 (10.3)	5 (4.6)	9 (9.6)
PERIPHERAL SENSORY NEUROPATHY	13 (12.1)	9 (8.4)	2 (1.9)	10 (10.6)
INSOMNIA	12 (11.2)	9 (8.4)	4 (3.7)	8 (8.5)
ABDOMINAL PAIN	7 (6.5)	7 (6.5)	4 (3.7)	7 (7.4)
BONE PAIN	11 (10.3)	10 (9.3)	-	4 (4.3)
EPISTAXIS	7 (6.5)	10 (9.3)	1 (0.9)	6 (6.4)
FEBRILE NEUTROPENIA	8 (7.5)	9 (8.4)	-	7 (7.4)
INFUSION RELATED REACTION	5 (4.7)	7 (6.5)	6 (5.6)	5 (5.3)
NAIL DISORDER	9 (8.4)	5 (4.7)	2 (1.9)	7 (7.4)
CONSTIPATION	8 (7.5)	8 (7.5)	3 (2.8)	3 (3.2)
ANAEMIA	7 (6.5)	3 (2.8)	5 (4.6)	6 (6.4)
CHILLS	6 (5.6)	4 (3.7)	10 (9.3)	-
OEDEMA PERIPHERAL	11 (10.3)	3 (2.8)	1 (0.9)	5 (5.3)
ABDOMINAL PAIN UPPER	5 (4.7)	6 (5.6)	1 (0.9)	7 (7.4)
COUGH	5 (4.7)	3 (2.8)	3 (2.8)	8 (8.5)
DRUG HYPERSENSITIVITY	2 (1.9)	6 (5.6)	6 (5.6)	5 (5.3)
MUSCULOSKELETAL PAIN	8 (7.5)	6 (5.6)	-	4 (4.3)
NEUROPATHY PERIPHERAL	9 (8.4)	5 (4.7)	-	4 (4.3)
PRURITUS	8 (7.5)	2 (1.9)	3 (2.8)	4 (4.3)
DIZZINESS	4 (3.7)	3 (2.8)	6 (5.6)	3 (3.2)
UPPER RESPIRATORY TRACT INFECTION	3 (2.8)	5 (4.7)	2 (1.9)	6 (6.4)
HAEMORRHOIDS	3 (2.8)	6 (5.6)	2 (1.9)	4 (4.3)
OROPHARYNGEAL PAIN	3 (2.8)	5 (4.7)	2 (1.9)	5 (5.3)
ACNE	2 (1.9)	6 (5.6)	2 (1.9)	4 (4.3)
HOT FLUSH	7 (6.5)	5 (4.7)	-	2 (2.1)
ERYTHEMA	2 (1.9)	4 (3.7)	2 (1.9)	5 (5.3)
URTICARIA	1 (0.9)	4 (3.7)	1 (0.9)	6 (6.4)
MENSTRUATION IRREGULAR	4 (3.7)	1 (0.9)	1 (0.9)	5 (5.3)
ALANINE AMINOTRANSFERASE INCREASED	6 (5.6)	1 (0.9)	-	3 (3.2)
FLUSHING	6 (5.6)	2 (1.9)	-	1 (1.1)
ASPARTATE AMINOTRANSFERASE INCREASED	6 (5.6)	-	-	2 (2.1)

Investigator text for Adverse Events encoded using MedDRA version 12.1.
Percentages are based on N.
Multiple occurrences of the same adverse event in one individual counted only once.
AE13 05MAR2010:05:40:34
Source: t_ae13_neo

In the adjuvant period, the most common AEs reported (i.e., those reported in ≥ 25% of patients in any treatment arm) were similar to those reported for the neoadjuvant period (e.g., nausea, neutropenia, fatigue, diarrhea and alopecia) with the exception of radiation skin injury, which occurred in similar proportions of patients across treatment arms (20.4% in the T+D arm, 18.6% in the Ptz+T+D arm, 23.4% in the Ptz+T arm, and 27.3% in the Ptz+D arm).

As of the third clinical cutoff date (12 July 2013), of the 378 patients who entered the post-treatment follow-up period, 7 patients (6.5%) in the T+D arm, 9 patients (8.4%) in the Ptz+T+D arm, 7 patients

(6.5%) in the Ptz+T arm, and 7 patients (7.4%) in the Ptz+D arm experienced AEs. Most of these occurred in the early post-treatment follow-up period (i.e., before the second clinical cutoff, 09 March 2012). LVD was reported in 3 patients (2.8%) in the Ptz+T+D arm and in 2 patients (2.1%) in the Ptz+D arm. Other common events included musculoskeletal and connective tissue disorders such as myalgia and arthralgia (experienced by 3 patients in the T+D arm and 2 patients in the Ptz+T+D arm) and gastrointestinal disorders (experienced by 4 patients in total: 1 patient in the T+D arm, 2 patients in the Ptz+T+D arm and 1 patient in the Ptz+T arm). Five AEs were reported between the second (9 March 2012) and third clinical cutoff date (12 July 2013) and all were considered unrelated to study treatment.

Study TRYPHAENA

In the neoadjuvant period, the most common SOCs affected (i.e., occurring in ≥ 25% across all treatment arms) were: Gastrointestinal Disorders, Skin and Subcutaneous Tissue Disorders, Blood and Lymphatic System Disorders, General Disorders and Administration Site Conditions, Infections and Infestations, Musculoskeletal and Connective Tissue Disorders, Respiratory, Thoracic and Mediastinal Disorders.

The incidence of AEs was highest in the Ptz+TCH arm (> 10% difference compared with both of the other two treatment arms) in the following SOC: General Disorders and Administration Site Conditions (61% in the Ptz+T+FEC/Ptz+T+D arm, 65% in the FEC/Ptz+T+D arm and 78% in the Ptz+TCH arm); Metabolism and Nutrition Disorders (24% in the FEC/Ptz+T+D arm, 16% in the FEC/Ptz+T+D arm and 34% in the Ptz+TCH arm); Investigations (19% in the FEC/Ptz+T+D arm, 13% in the FEC/Ptz+T+D arm and 33% in the Ptz+TCH arm).

The incidence of patients with Cardiac Disorders was lowest in the FEC/Ptz+T+D arm compared with the Ptz+T+FEC/Ptz+T+D arm and Ptz+TCH arm (5.3%, vs. 11.1% and 10.5%, respectively). LVD was the most frequently reported event (4 patients [5.6%] in the Ptz+T+FEC/Ptz+T+D arm, 3 patients [4.0%] in the FEC/Ptz+T+D arm and 2 patients [2.6%] in the Ptz+TCH arm).

The majority of patients who entered the adjuvant period experienced at least one AE (57/68 [84%] in the Ptz+T+FEC/Ptz+T+D arm, 60/65 [92%] in the FEC/Ptz+T+D arm and 53/67 [79%] in the Ptz+TCH arm). The most common SOCs affected (i.e., in ≥25% of patients across all 3 treatment arms) were Musculoskeletal and Connective Tissue Disorders (33.8% in the Ptz+T+FEC/Ptz+T+D arm vs. 40.0% in the FEC/Ptz+T+D arm vs. 32.8% in the Ptz+TCH arm), and Skin and Subcutaneous Tissue Disorders (26.5% in the Ptz+T+FEC/Ptz+T+D arm vs. 36.9% in the FEC/Ptz+T+D arm vs. 32.8% in the Ptz+TCH arm). Across treatment arms, the most common AE was radiation skin injury (11/68 [16.2%] in the Ptz+T+FEC/Ptz+T+D arm, 14/65 [21.5%] in the FEC/Ptz+T+D arm, 7/67 [10.4%] in the Ptz+TCH arm).

In general, the most common SOCs affected and most frequently occurring AEs in the overall treatment period were similar to those reported for the neoadjuvant and adjuvant periods. In the overall treatment period, the incidence of patients with Cardiac Disorders was comparable between the Ptz+T+FEC/Ptz+T+D arm and the FEC/Ptz+T+D arm (15.3% vs. 16.0%), with a slightly higher frequency reported in the Ptz+TCH arm (21.1%). The most frequently reported AEs occurring in the SOC, Cardiac Disorders were LVD, palpitations and tachycardia.

In the post-treatment follow-up period, 6 patients (8.3%) in the Ptz+T+FEC/Ptz+T+D arm, 9 patients (12.0%) in the FEC/Ptz+T+D arm and 5 patients (6.6%) in the Ptz+TCH arm experienced AEs. During this period, the most common AE (occurring in more than 2% of patients in any treatment arm) was LVD (1.4% of patients in the Ptz+T+FEC/Ptz+T+D arm, 4.0% in the FEC/Ptz+T+D arm, and 2.6% in the Ptz+TCH arm). All other events occurred in single patients.

Study CLEOPATRA

As of the clinical cutoff date of 14 May 2012, the overall incidence of AEs was balanced between the treatment arms (98.7% of patients in the Pla+T+D arm vs. 100% of patients in the Ptz+T+D arm), although the total number of AEs reported in the Ptz+T+D arm (6521 AEs) was higher than in the Pla+T+D arm (5535 AEs). The majority of AEs in both treatment arms were Grade 1-2 in severity: 4890 of 5535 AEs (88.3%) in the Pla+T+D arm and 5773 of 6521 AEs (88.5%) in the Ptz+T+D arm.

In both treatment arms, the most common AEs (i.e., occurring in ≥ 25% of patients in either arm) included alopecia, diarrhoea, neutropenia, nausea, fatigue, rash, asthenia, decreased appetite, vomiting, peripheral edema and mucosal inflammation.

The incidence of diarrhoea, rash, mucosal inflammation, pruritus, febrile neutropenia and dry skin was higher (≥ 5% difference) in the Ptz+T+D arm compared with the Pla+T+D arm, whereas the incidence of peripheral edema and constipation was higher (≥ 5% difference) in the Pla+T+D arm compared with the Ptz+T+D arm.

Overall, 17.4% of patients in the Pla+T+D arm (69 patients) and 15.4% of patients in the Ptz+T+D arm (63 patients) experienced Cardiac Disorders. The most frequently reported cardiac-related AE was LVD (8.6% of patients in the Pla+T+D arm vs. 5.4% of patients in the Ptz+T+D arm).

The majority of patients in both treatment arms experienced at least one AE considered by the Investigator to have a reasonable suspected causal relationship to study treatment (96.2% of patients in the Pla+T+D arm and 97.3% of patients in the Ptz+T+D arm). The most commonly reported AEs that were considered related to study treatment by the Investigator were alopecia, diarrhoea, nausea, neutropenia, fatigue, rash, asthenia, mucosal inflammation, decreased appetite, nail disorder and myalgia.

The post-treatment follow-up period in the CLEOPATRA study was defined as starting more than 42 days after discontinuation of study medication. During the post-treatment follow-up period, 12 patients (3.0%) and 10 patients (2.5%) reported a total of 14 and 19 AEs in the Pla+T+D and Ptz+T+D arms, respectively. One event, Prinzmetal angina in a patient in the Pla+T+D arm, was considered serious and related to study treatment. All other AEs reported during this period were non-serious, and no notable difference in incidence of AEs was observed between the treatment arms.

Adverse events grade ≥ 3

Study NEOSPHERE

During the neoadjuvant period, the majority of patients (62.6%-72.9%) in the docetaxel-containing treatment arms (i.e., T+D, Ptz+T+D, and Ptz+D arms) experienced at least one AE of Grade ≥ 3 severity compared with 6.5% in the Ptz+T arm. The majority of Grade ≥ 3 AEs were Blood and Lymphatic System Disorders (mainly neutropenia and leukopenia), and these were reported by fewer patients in the Ptz+T+D arm compared with the T+D or Ptz+D arms.

As expected, during the adjuvant period, the incidence of Grade ≥ 3 AEs was highest in the Ptz+T arm (67.0%, compared with 35.9% in the T+D arm, 35.3% in the Ptz+T+D arm and 38.6% in the Ptz+D arm, which was likely due to the administration of 3 cycles of docetaxel (in addition to 3 cycles of FEC) during the adjuvant period in this arm (all other arms received docetaxel in the neoadjuvant period only). The most common Grade ≥ 3 AEs (i.e., those reported in > 5% of patients in any treatment arm) were haematological toxicities: neutropenia, febrile neutropenia and granulocytopenia.

During adjuvant trastuzumab treatment following the completion of adjuvant chemotherapy, 8 patients (7.8%) in the T+D arm, 8 patients (7.8%) in Ptz+T+D arm, 10 patients (10.6%) in the Ptz+T arm and 8 patients (9.1%) in the Ptz+D arm experienced Grade ≥ 3 AEs.

During the overall treatment period, Grade ≥ 3 AEs were generally balanced across treatment arms during the study, with the lowest incidence occurring in the Ptz+T arm (60.2%, compared with 81.3% in the T+D arm, 72.9% in the Ptz+T+D arm and 78.7% in the Ptz+D arm).

The most common Grade ≥ 3 AEs (i.e., those reported in ≥ 5% of patients in any treatment arm) were neutropenia, febrile neutropenia, leukopenia, irregular menstruation and diarrhea. Of note, in the Ptz+T arm, although the incidence of Grade ≥ 3 febrile neutropenia was lowest (4.6%) compared with the other treatment arms, the incidence of Grade ≥3 granulocytopenia was highest (4.6%).

Three Grade 3 events (no Grade 4 or 5 events) were reported in the post-treatment follow-up period: one event of abdominal distention in a patient in the T+D arm (which was considered unrelated to study treatment and remained unresolved at the time of the clinical cutoff date); one event of myeloproliferative disorder in a patient in the Ptz+D arm; and one event of 'breast prosthesis removal' in a patient in the Ptz+D arm.

Study TRYPHAENA

During the neoadjuvant period, the proportion of patients experiencing an AE of Grade ≥ 3 severity was 69% in the Ptz+T+FEC/Ptz+T+D arm, 60% in the FEC/Ptz+T+D arm and 74% in the Ptz+TCH arm. Grade ≥ 3 AEs were predominately Blood and Lymphatic System Disorders, with neutropenia the most commonly reported event (43%–47% of patients across treatment arms), followed by febrile neutropenia (18.1% of patients in the Ptz+T+FEC/Ptz+T+D arm, 9.0% of patients in the FEC/Ptz+T+D arm and 17.1% of patients in the Ptz+TCH arm). Grade ≥ 3 Infection and Infestation AEs occurred in 4%–8% of patients across treatment arms, with no single event predominating. Grade ≥ 3 neutropenic infection occurred in 2 patients (1 each in the FEC/Ptz+T+D arm and the Ptz+TCH arm), and Grade ≥ 3 neutropenic sepsis occurred in one patient (in the Ptz+TCH arm). Grade ≥ 3 anemia was notably higher in the Ptz+TCH arm (17%) than in the Ptz+T+FEC/Ptz+T+D and FEC/Ptz+T+D arms (1% and 3%, respectively). Grade ≥ 3 thrombocytopenia also occurred exclusively in patients in the Ptz+TCH arm (11.8% of patients), which led to dose modification of study treatment in some patients. Grade ≥ 3 LVD occurred in only two patients (2.7%), both in the FEC/Ptz+T+D arm.

Of the patients who entered the adjuvant period, a total of 9 patients in the Ptz+T+FEC/Ptz+T+D arm, 10 patients in the FEC/Ptz+T+D arm and 8 patients in the Ptz+TCH arms experienced a Grade ≥ 3 AE in the adjuvant period. One fatal event was reported ("metastatic neoplasm", which appeared to be due to relapse of the patient's underlying breast cancer), and occurred in a patient in the Ptz+T+FEC/Ptz+T+D arm. All other events were Grade 3 and occurred in single patients, with the exception of erythema (2 patients in the Ptz+T+FEC/Ptz+T+D arm), pneumonia (2 patients in the Ptz+T+FEC/Ptz+T+D arm) and neutropenia (2 patients in the Ptz+T+FEC/Ptz+T+D arm, 3 in the FEC/Ptz+T+D arm and 1 in the Ptz+TCH arm).

In the overall treatment period, the proportion of patients experiencing an AE of Grade ≥ 3 was similar to that seen during the neoadjuvant period (73.6% in the Ptz+T+FEC/Ptz+T+D arm, 61.3% in the FEC/Ptz+T+D arm and 73.7% in the Ptz+TCH arm).

Two Grade ≥ 3 events were reported in the post-treatment follow-up period, both in the FEC/Ptz+T+D arm: one patient experienced NYHA Class II symptomatic LVSD (NCI-CTCAE Grade 3), which later improved, and one patient (who received docetaxel in the post-treatment follow-up period) experienced a Grade 4 event of neutropenic infection, which resolved without sequelae.

Study CLEOPATRA

t_ae11_345 Summary of NCI-CTCAE Grade 3, 4 or 5 Adverse Events by Body System and Trial Treatment
Protocol(s): WO20698
Analysis: SAFETY (BY TREATMENT RECEIVED) Center: ALL CENTERS
Snapshot Date: 01JUN2012 Clinical Cut-Off Date: 14MAY2012

Body System/ Adverse Event	Placebo + Trastuzumab + Docetaxel N = 396 No. (%)	Pertuzumab + Trastuzumab + Docetaxel N = 408 No. (%)
ALL BODY SYSTEMS		
Total Pts with at Least one AE	291 (73.5)	311 (76.2)
Total Number of AEs	594	668
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
Total Pts With at Least one AE	215 (54.3)	241 (59.1)
NEUTROPENIA	182 (46.0)	200 (49.0)
LEUKOPENIA	59 (14.9)	50 (12.3)
FEBRILE NEUTROPENIA	30 (7.6)	56 (13.7)
ANAEMIA	14 (3.5)	10 (2.5)
GRANULOCYTOPENIA	9 (2.3)	6 (1.5)
THROMBOCYTOPENIA	2 (0.5)	-
LYMPHOPENIA	-	1 (0.2)
Total Number of AEs	296	323

Investigator text for Adverse Events encoded using MedDRA version 15.0.
Percentages are based on N.
Multiple occurrences of the same adverse event in one individual counted only once.
AE11 13AUG2012:01:22:46 (1 of 14)

Adverse Events of Special Interest (AESI)

Cardiac dysfunction

Reporting of cardiac safety was similar but not identical in the three studies. Although Investigators were to report left ventricular dysfunction events as asymptomatic or symptomatic LVSD in the TRYPHAENA and CLEOPATRA studies, these events were both coded to 'left ventricular dysfunction' (LVD), according to MedDRA. Symptomatic LVD is distinguishable from asymptomatic LVD in these studies by NCICTCAE grading (symptomatic events are Grade 3 or greater). In the NEOSPHERE study, symptomatic LVSD was reportable as 'congestive heart failure' (CHF), which coded to the term, 'heart failure, congestive' according to MedDRA. In all three studies, asymptomatic declines in LVEF were only reportable as AEs (using the term, 'left ventricular systolic dysfunction' [LVSD]) if they met certain criteria. However, if an event met any criteria for seriousness (e.g., hospitalization), this was reportable as an SAE.

When analyzing the data, SAEs considered suggestive of CHF were defined as SAEs coded to a preferred term (PT) in the standardized MedDRA query (SMQ) 'Cardiac Failure (wide).' This included symptomatic events reported as SAEs under the term LVSD (MedDRA PT LVD), as well as other events reported as SAEs (such as pulmonary edema, paroxysmal nocturnal dyspnea, etc).

Study NEOSPHERE

To ensure that differences in cardiac safety profile in the four arms of the study were not due to imbalances in potential risk factors at baseline, these were compared and no major imbalances between the treatment arms were apparent.

Cardiac events

In the Neoadjuvant Period, there were slightly more cardiac disorders in Arm B (Ptz+T+D), but these were mostly palpitations in relation with infusions. 5 patients (4.7%) in the T+D arm, 12 patients (11.2%) in the Ptz+T+D arm, 6 patients (5.6%) in the Ptz+T arm and 3 patients (3.2%) in the Ptz+D arms experienced at least one AE in the SOC, Cardiac Disorders. Many of these events were

palpitations or tachycardia, and some of these occurred on the day of a study treatment infusion, suggesting they were infusion-related events. There were 3 cases of left ventricular dysfunction.

In the Adjuvant Period, the proportion of patients with AEs in the SOC, Cardiac Disorders was highest in the Ptz+T+D arm (12.7%) and lowest in the T+D arm (3.9%). The most common cardiac AEs were LVD and palpitations, each reported in 11 patients. Of the 11 patients with LVD in the adjuvant period (1 in the T+D arm, 5 in the Ptz+T+D arm, 0 in the Ptz+T arm and 5 in the Ptz+D arm), all events resolved without sequelae, with the exception of one patient in the Ptz+D arm, for whom palpitations remained unresolved. Overall, there were also more cardiac disorders in Arm B, with 5 cases of left ventricular dysfunction. In contrast to the neoadjuvant period, the risk of LVD seemed to be slightly increased in Arm D (Ptz+D) in the adjuvant setting.

During the overall treatment period, the incidence of LVD was higher in the pertuzumab, trastuzumab and docetaxel-treated group (7.5%) compared to the trastuzumab and docetaxel-treated group (1.9%). There was one case of symptomatic LVD in the Perjeta and trastuzumab-treated group. Only two patients had a Grade ≥3 LVD; one patient in each of Arm B (Ptz+T+D) and Arm C (Ptz+T). Similarly, only two patients experienced a LVD leading to withdrawal from study treatment.

Looking at potential risk factors, several of the patients had a history of hypertension and hypercholesterolemia/dyslipidemia, and were being treated with antihypertensiva and statins. The majority of the events were asymptomatic.

There were few cases of LVD in the follow-up period. Those few cases that occurred were not serious and resolved without sequelae.

In conclusion, there were more cases of LVD in the Ptz+T+D arm, but these were only Grade 3, asymptomatic and in some cases seen in patients with cardiac risk factors.

Changes in Left Ventricular Ejection Fraction during the NEOSPHERE Study

To enter the study, patients had to have an LVEF of ≥55%. Patients in all four treatment arms had mean and median LVEF values of about 65% at baseline (individual patient values range from 53%-81%). The majority of patients (~60%-70%) in all four treatment arms had no change in LVEF over the overall treatment period.

The greatest decline in LVEF was around 7-8%, and most of the patients remained above 50% in LVEF. About 20 patients experienced a decline more than 10%. Of these, 9 patients had a decline in LVEF on two consecutive LVEF measurements. LVEF decline seemed to be small and only a fraction of the patients experience more than 10% on two consecutive measurements.

Study TRYPHAENA

Cardiac events

In the neoadjuvant period, 8 patients (11.1%) in the Ptz+T+FEC/Ptz+T+D arm, 4 patients (5.3%) in the FEC/Ptz+T+D arm and 8 patients (10.5%) in the Ptz+TCH arm, experienced at least one AE in the SOC, Cardiac Disorders. As seen in the NEOSPHERE study, the most common cardiac AEs were LVD and palpitations, with all other events occurring in two patients or fewer. Overall, there were less AEs in Arm B, but the number of LVD is more or less comparable between the three arms.

In the adjuvant period, a total of 27 patients (5 [7.4%] in the Ptz+T+FEC/Ptz+T+D arm, 10 patients [15.4%] in the FEC/Ptz+T+D arm and 12 patients [17.9%] in the Ptz+TCH arm) experienced at least one AE in the SOC, Cardiac Disorders. Of these, 4 patients (5.9%) in the Ptz+T+FEC/Ptz+T+D arm, 5 patients (7.7%) in the FEC/Ptz+T+D arm and 3 patients (4.5%) in the Ptz+TCH arm experienced LVD,

including one patient in the Ptz+TCH arm who experienced symptomatic LVSD (assessed by Investigator as being NYHA Class II; NCI-CTCAE Grade 3).

During the overall treatment period, the incidence of LVD (during the overall treatment period) was 8.3% in the group treated with Perjeta plus trastuzumab and FEC (followed by Perjeta plus trastuzumab and docetaxel); 9.3% in the group treated with Perjeta plus trastuzumab and docetaxel following FEC; and 6.6% in the group treated with Perjeta in combination with TCH. The incidence of symptomatic LVD (congestive heart failure) was 1.3% in the group treated with Perjeta plus trastuzumab and docetaxel following FEC (this excludes a patient who experienced symptomatic LVD during FEC treatment prior to receiving Perjeta plus trastuzumab and docetaxel) and also 1.3% in the group treated with Perjeta in combination with TCH. No patients in the group treated with Perjeta plus trastuzumab and FEC followed by Perjeta plus trastuzumab and docetaxel experienced symptomatic LVD (see SmPC section 4.8).

The primary endpoints of study TRYPHAENA were:

- Incidence of symptomatic cardiac events as assessed by the Investigator (Grade 3, 4 or 5 symptomatic LVSD)

- Clinically significant LVEF declines over the course of the neoadjuvant period (LVEF decline of ≥10% from baseline and to a value of <50%)

Following exposure to the study treatment, three patients (none in Arm A (Ptz+T+FEC/Ptz+T+D), 2 in Arm B (FEC/Ptz+T+D) and 1 in Arm C (Ptz+TCH)) experienced symptomatic LVSD. Only one of these events occurred in the neoadjuvant treatment period (Arm B) during FEC treatment and prior to pertuzumab, and a single event presented in the adjuvant period (Arm C) and in the post-treatment follow-up period (Arm B).

The majority of patients who experienced LVEF declines of at least 10%-points from baseline to below 50% were observed on local readings (5 patients in Arm A, 9 patients in Arm B and 7 patients in Arm C). The central LVEF readings identified 4 patients (3 in Arm B and 1 in Arm C) with significant LVEF declines that were not identified on local readings.

Nine patients (2 in Arm A, 5 in Arm B and 2 in Arm C) had declines in LVEF of at least 10%-points from baseline to below 50%, during the post-treatment follow-up period. One of these 9 patients (in Arm B) had experienced an LVEF decline during the adjuvant treatment period, which continued into the post-treatment follow-up period; 3 of these 9 patients (2 in Arm A and 1 in Arm B) had experienced a previous LVEF decline with recovery to ≥ 50% during study treatment.

Mean LVEF dropped to below baseline during treatment in all three treatment arms, however, mean decreases were less than 5%-points in all cases, for values based on local readings and no more than 8%-points for values based on central readings. The profile for mean change in LVEF from baseline was similar in the three treatment arms. In general, the decline was greatest at Cycle 6.

Table 36: Total cardiac events during neoadjuvant, adjuvant and post treatment follow-up periods

	Arm A: FEC+P+T x3/ DOC+P+T x3 N= 72	Arm B: FEC x3/ DOC+P+T x3 N=75	Arm C: TCH+P x6 N= 76
Total number of patients with a local LVEF decline	5 (6.6%)	9 (12%)	7 (9.2%)
Total number of patients with a central LVEF decline only	0	3 (4.0%)	1 (1.3%)
Total number of patients with a local and/or central LVEF decline	5 (6.6%)	12 (16.0%)	8 (10.5%)
Total number of AE PT 'LVD': *Grade ≥3 (i.e., symptomatic LVSD)*	0	2 (2.7%)[a]	1 (1.3%)
Number of AE PT 'LVD' *Grade ≥3 ongoing as of 22 Jul 2013*	0	1 (1.3%)[b]	0

[a] Patient 158959/3288 (who had symptomatic LVSD during FEC and prior to the administration of pertuzumab, trastuzumab and docetaxel) is excluded
[b] Patient 158981/3580 is asymptomatic and continues to be monitored.
Source: page 128

Overall, there were only very few cases of symptomatic LVSD, and no sign of any difference between the treatment arms. There were slightly more patients with LVEF decline in Arm B (FEC/Ptz+T+D) and C (Ptz+TCH).

Study CLEOPATRA

Cardiac Events

At the time of the clinical cutoff of 14 May 2012, the proportion of patients who had AEs during the study treatment period in the SOC, Cardiac Disorders was comparable between treatment arms (17.4% of patients in the Pla+T+D arm vs. 15.4% of patients in the Ptz+T+D arm), despite longer time on study treatment in the Ptz+T+D arm. LVD was the most common cardiac AE reported, with 34 patients (8.6%) experiencing LVD AEs in the Pla+T+D arm, and 22 patients (5.4%) in the Ptz+T+D arm. As seen in the NEOSPHERE and TRYPHAENA studies, palpitations and tachycardia were the most frequently reported cardiac AEs, other than LVD. The proportion of patients experiencing Grade ≥ 3 LVD (13 patients [3.3%] vs. 5 patients [1.2%]) was higher in the Pla+T+D arm vs. the Ptz+T+D arm, although symptomatic LVD and LVD reported as an SAE was balanced between the two treatment arms. The proportion of patients who experienced cardiac SAEs overall was also higher in the Pla+T+D arm (3.5% of patients) than in the Ptz+T+D arm (1.7% of patients).

Overall, there were equal numbers of cardiac disorders in the two arms. However, the incidence of LVD during study treatment was higher in the placebo-treated group than in the Perjeta-treated group (8.6% and 5.4%, respectively). The incidence of symptomatic LVD was also lower in the Perjeta treated group (1.8% in the placebo-treated group vs. 1.2% in the Perjeta-treated group) (see section 4.8).

Comparison of Cardiac Dysfunction between the three Studies

Table 37: Key cardiac safety data from the NEOSPHERE, TRYPHAENA and CLEOPATRA studies

Safety Parameter	Patients Experiencing Event								
	NEOSPHERE (overall treatment period)				TRYPHAENA (overall treatment period)			CLEOPATRA (overall treatment period)	
	T+D n=107	Ptz+T+D n=107	Ptz+T n=108	Ptz+D n=94	Ptz+T+FEC/ Ptz+T+D n= 72	FEC/ Ptz+T+D n=75	Ptz+TCH n=76	Pla+T+D n=396	Ptz+T+D n=408
Any cardiac AE*	7.5%	20.6%	14.8%	12.8%	15.3%	16.0%	21.1%	17.4%	15.4%
LVSD (PT)	1.9%	7.5%	0	5.3%	8.3%	9.3%	6.6%	8.6%	5.4%
Gr≥3 LVSD (PT)	0	0.9%***	0	0	0	2.7%	1.3%	3.3%	1.2%
LVEF decline**	1.9%	7.5%	0.9%	5.3%	6.9%	13.3%	7.9%	6.6%	3.8%
CHF SAE	0	2.8%***	0.9%	0	1.4%	2.7%	1.3%	2.0%	1.5%

AE = adverse event; CHF = congestive heart failure (symptomatic left ventricular dysfunction) SAEs analyzed by SMQ (wide) 'Cardiac failure'; LVEF = left ventricular ejection fraction; LVSD = left ventricular systolic dysfunction; PT = preferred term; SAE = serious adverse event.

Shaded columns show comparative data for Ptz+T+D vs T+D (+placebo).

* Any AE in the Cardiac Disorder SOC.

** LVEF decline of ≥ 10% from baseline to an absolute value <50%.

*** Reported as an SAE suggestive of CHF, however, events were asymptomatic.

Derived from: for NEOSPHERE - Tables 34, 35, 37, and 39 and t_ae11_345 of Update CSR1;

for TRYPHAENA - Tables 7, 14, 15, and 17 of the Update CSR1 for TRYPHAENA;

for CLEOPATRA Tables 37, 38, 39 and 42 of the Update CSR.

Table 38: Cardiac events, LVD and LVEF declines with confidence intervals in the NEOSPHERE, TRYPHAENA and CLEOPATRA studies

Safety Parameter	Patients Experiencing Event								
	NEOSPHERE (overall treatment period)				TRYPHAENA (overall treatment period)			CLEOPATRA (overall treatment period)	
	T+D n=107	Ptz+T+D n=107	Ptz+T n=108	Ptz+D n=94	Ptz+T+FEC/ Ptz+T+D n= 72	FEC/ Ptz+T+D n=75	Ptz+TCH n=76	Pla+T+D n=396	Ptz+T+D n=408
Cardiac Disorder AE[1]									
Incidence (% pts)	7.5	20.6	14.8	12.8	15.3	16.0	21.1	17.4	15.4
95% CI	3.3;14.2	13.4;29.5	8.7;22.9	6.8;21.2	7.9;25.7	8.6;26.3	12.5;31.9	13.8;21.5	12.1;19.3
LVD[2]									
Incidence (% pts)	1.9	7.5	0.9	5.3	8.3	9.3	6.6	8.6	5.6
95% CI	0.2;6.6	3.3;14.2	0.0;5.1	1.7;12.0	3.1;17.3	3.8;18.3	2.2;14.7	6.0;11.8	3.6;8.3
LVEF Decline[3]									
Incidence (% pts)	1.9	8.4	0.9	7.4	6.9	14.7	10.5	7.1	4.9
95% CI	0.2;6.6	3.9;15.4	0.0;5.1	3.0;14.7	2.3;15.5	7.6;24.7	4.7;19.7	4.7;10.1	3.0;7.5

AE=adverse event; LVEF=left ventricular ejection fraction; LVD=left ventricular dysfunction.

Shaded columns: Ptz+T+D and T+D regimens

[1] Incidence of any cardiac events where the SOC of the reported AE is 'Cardiac Disorders' - treatment period only.

[2] Incidence of any LVD event where the reported AE preferred term is 'Left Ventricular Dysfunction' - treatment period only. For NEOSPHERE, the preferred term 'Cardiac Failure Congestive' was also included.

[3] Incidence of any significant LVEF declines where LVEF < 50% and ≥ 10%-points decrease from baseline - including treatment-free follow-up period. The reporting period is different to that given for LVEF declines in the previous table (Table 65).

Source: Derived from t_rrcardev_s for NEOSPHERE; t_rrcardev_s for TRYPHAENA and t_rrcardev_s for CLEOPATRA.

Infusion-related Reactions

Study NEOSPHERE: The overall incidence and pattern of infusion-related reactions were comparable between the pertuzumab containing arms. There were very few Grade 3 or 4 AEs.

Study TRYPHAENA: More AEs were observed in Arm C (Ptz+TCH), but the number of Grade 3 or 4 AEs was comparable between the three arms.

Study CLEOPATRA: The overall incidence was slightly higher in the Ptz+T+D arm, and only 1 Grade 3/4 AE was observed in each arm. However, the incidence of infusion-related reactions was considerable higher in the NEOSPHERE and TRYPHAENA compared to the CLEOPATRA study.

In the NEOSPHERE and TRYPHAENA trials in the neoadjuvant setting, Perjeta was administered on the same day as the other study treatment drugs in all cycles. Overall, infusion reactions were consistent with those observed in CLEOPATRA at the cycles when Perjeta was given on the same day as trastuzumab and docetaxel, with a majority of reactions being mild or moderate (see SmPC section 4.8).

Anaphylaxis and hypersensitivity

Study NEOSPHERE: There were few cases of anaphylaxis and hypersensitivity. The majority of the AEs were Grade 1-2. Only three patients experienced a Grade 3 AE (2 AEs were attributed to docetaxel).

Study TRYPHAENA: Only 1 AE was observed in Arm B (FEC/Ptz+T+D). In Arm A (Ptz+T+FEC/Ptz+T+D) and C (Ptz+TCH) comparable numbers were observed (7 (9.7%) vs. 10 (13.2%). Patients in Arm B received only three doses of pertuzumab and trastuzumab, which may explain the incidence rate.

Study CLEOPATRA: The incidence was comparable between the two treatment arms, and the majority of cases were mild.

In NEOSPHERE and TRYPHAENA trials in the neoadjuvant setting, hypersensitivity/anaphylaxis events were consistent with those observed in CLEOPATRA. In NEOSPHERE, two patients in the Perjeta and docetaxel-treated group experienced anaphylaxis. In TRYPHAENA, the overall frequency of hypersensitivity/anaphylaxis was highest in the Perjeta and TCH treated group (13.2%), of which 2.6% were NCI-CTCAE v.3 Grade 3-4 (see SmPC section 4.8).

Leukopenia and Leukopenic Infection Events

Study NEOSPHERE:

The overall incidence rate of blood and lymphatic system disorders was comparable between Arm A (T+D) and D (Ptz+D). The incidence rate was slightly lower in Arm B. There was only one event in Arm C (Ptz+T), which reflects the fact that these AEs are associated with chemotherapy. Only one patient, in Arm D, discontinued treatment. Febrile neutropenia rates were similar across Arm A (T+D), B (Ptz+T+ D) and D (Ptz+D). 8.4% of patients treated with neoadjuvant Perjeta, trastuzumab and docetaxel experienced febrile neutropenia compared with 7.5% of patients treated with trastuzumab and docetaxel. There were few events of infections.

As in the CLEOPATRA study, a higher incidence of neutropenia and febrile neutropenia was observed among Asian patients compared with other patients in both neoadjuvant trials. In NEOSPHERE, 8.3% of Asian patients treated with neoadjuvant Perjeta, trastuzumab and docetaxel experienced febrile neutropenia compared with 4.0% of Asian patients treated with neoadjuvant trastuzumab and docetaxel (see SmPC section 4.8).

Study TRYPHAENA: The overall incidence was slightly lower in Arm B (FEC/Ptz+T+D); However, the rate of neutropenia was comparable across the three arms. Febrile neutropenia occurred less frequently in Arm B. Febrile neutropenia occurred in 17.1% of patients treated with neoadjuvant Perjeta + TCH, and 9.3% of patients treated with neoadjuvant Perjeta, trastuzumab and docetaxel following FEC. The incidence of febrile neutropenia was higher in patients who received six cycles of Perjeta compared with patients who received three cycles of Perjeta, independent of the chemotherapy given (see SmPC section 4.8).

Study CLEOPATRA:
The overall incidence was comparable between the two arms and the incidence of neutropenia and febrile neutropenia in the Ptz+T+D arm were comparable to the Ptz+T+D arm in the NEOSPHERE

study. In conclusion, there is no indication of any excess cases of neutropenia or febrile neutropenia by adding pertuzumab to trastuzumab in the neoadjuvant setting.

Diarrhoea

Study NEOSPHERE: In the neoadjuvant period, the incidence of diarrhoea was higher in the Ptz+T+D arm (85 episodes in 49 patients [45.8%]) and the Ptz+D arm (72 episodes in 51 patients [54.3%]) than in the T+D and Ptz+T arms (49 and 48 episodes in 36 patients [33.6%]) and 30 patients [27.8%], respectively. Overall, 51.4% of the patients in Arm B experienced diarrhoea. In Arm A and C the incidences were lower. Most events were mild to moderate in severity. The incidence of Grade ≥ 3 AEs was low and comparable across treatment arms.

Study TRYPHAENA: Diarrhoea was most common Arm C (Ptz+TCH) and in the neoadjuvant period, and less common in the adjuvant period. Diarrhoea occurred in 72.3% of patients treated with neoadjuvant Perjeta+TCH and 61.4% of patients treated with neoadjuvant Perjeta, trastuzumab and docetaxel following FEC. Most events were mild to moderate in severity (see SmPC section 4.8).

Study CLEOPATRA: The incidence of diarrhoea was highest in the experimental (68.1%) arm and was often observed in the first cycle.

In conclusion, the overall incidence rate of diarrhoea was lower in Arm B (Ptz+T+D) in the NEOSPHERE study compared to the experimental arm in the CLEOPATRA study, which is reassuring.

Rash

In the NEOSPHERE trial, rash occurred in 40.2% of patients treated with neoadjuvant Perjeta, trastuzumab and docetaxel compared with 29.0% of patients treated with trastuzumab and docetaxel.

The overall incidence rate of Grade ≥ 3 AEs was low and comparable between the Arms A (T+D), B (Ptz+T+D) and D (Ptz+D), while it was even lower in Arm C (Ptz+T).

In the TRYPHAENA trial, rash occurred in 36.8% of patients treated with neoadjuvant Perjeta + TCH and 20.0% of patients treated with neoadjuvant Perjeta, trastuzumab and docetaxel following FEC. The incidence of rash was higher in patients who received six cycles of Perjeta compared with patients who received three cycles of Perjeta, independent of the chemotherapy given.

These results were comparable with the experimental arm in the CLEOPATRA study, which suggested that there is no increased risk of adding pertuzumab to trastuzumab in the neoadjuvant setting.

Mucositis

In NEOSPHERE, mucositis was common during the neoadjuvant and adjuvant treatment periods (33.6% and 24.3% of patients in the T+D arm, 45.8% and 30.4% in the Ptz+T+D arm, 9.3% and 39.4% in the Ptz+T arm and 43.6% and 25.0% in the Ptz+D arm respectively). Only 2 patients experienced Grade ≥ 3 mucositis (1 in the Ptz+T+D arm and 1 in the Ptz+D arm).

Overall, 46.7% of patients in the T+D arm, 54.2% in the Ptz+T+D arm, 38.9% in the Ptz+T arm and 50.0% in the Ptz+D arm experienced mucositis, but only 4 patients experienced Grade > 3 mucositis at any time (3 in the Ptz+T+D arm and 1 in the Ptz+D arm).

During the neoadjuvant period, 45.8% of patients in the Ptz+T+FEC/Ptz+T+D arm, 41.3% of patients in the FEC/Ptz+T+D arm and 34.2% of patients in the Ptz+TCH arm experienced mucositis (t_ae15_muc_neo). Most of these were Grade 1-2 in severity. Only 1, 2 and 1 patient experienced a Grade 3 mucositis event in the Ptz+T+FEC/Ptz+T+D, FEC/Ptz+T+D and Ptz+TCH arms, respectively.

As in the NEOSPHERE study, mucosal inflammation and stomatitis were the most frequently reported events

Mucositis is a common AESI, and most frequently observed in the experimental arm of the CLEOPATRA study, when comparing all three studies. This AE occurred much less frequently in the Ptz+T arm of the NEOSPHERE study, thus indicating that it is closely associated with chemotherapy.

Interstitial Lung Disease

Very few and sporadic cases were observed. No firm conclusions can be drawn.

Hepatic Disorders

Very few cases were observed in the NEOSPHERE and TRYPHAENA studies. One patient in the TRYPHAENA study withdrew from treatment due to Grade 2 ASAT, Grade 3 ALAT and Grade 3 GGT abnormalities. Event rates were low and comparable in the CLEOPATRA study. However, one event of fulminant hepatitis had a fatal outcome (please see under "Deaths"). It is difficult to draw any conclusions, but pertuzumab does not seem to have hepatotoxic effects when added to trastuzumab in the neoadjuvant setting.

Venous Thromboembolic Events

As of the clinical cutoff date of 12 July 2013 in the NEOSPHERE study, 4 patients (1.0%) experienced VTEs during the study overall: 2 in the Ptz+T+D arm (1.9% of patients) and 2 in the Ptz+D arm (2.1% of patients), one of which was Grade > 3. Two of these events were reported in the neoadjuvant period and 2 in the adjuvant period.

In the TRYPHAENA study, overall, 4 patients (1.8%) experienced VTEs in the TRYPHAENA study; 3 patients in the neoadjuvant period (2 patients in the Ptz+T+FEC/Ptz+T+D arm and 1 patient in the Ptz+TCH arm) and 1 patient in the adjuvant period (in the FEC/Ptz+T+D).

VTE occurred more frequently in the experimental arm in the CLEOPATRA study. However, only very few cases have been observed in the two neoadjuvant studies to draw any conclusions.

Serious adverse event / deaths / other significant events

Deaths

In the neoadjuvant period one patient died (NEOSPHERE) of fulminant hepatitis. This patient had a history of obesity, diabetes and hypertension, and was being treated for these conditions. However, the patient was admitted to a local hospital and no liver biopsy nor hepatitis serology were performed. Also, no autopsy was performed. Furthermore, there are also uncertainties with regard to the treatment received at the local hospital. Hepatic failure was not observed in the experimental arm of the CLEOPATRA study.

The other two deaths in the neoadjuvant period in the NEOSPHERE study were due to PD and metastases.

There were no non-PD deaths in the TRYPHAENA study and 6 non-PD deaths in the NEOSPHERE study. Four cases had "unknown" reason and two cases were due to primary colorectal cancer.

In the post-treatment follow-up period, 25 (NEOSPHERE) and 12 (TRYPHAENA) deaths occurred. The majority of deaths were assessed as unrelated or "not known" in relation to trial treatment. In the NEOSPHERE follow up treatment period the MAH did not report the cause of death for 4 patients but classified the events as not related to study treatment.

Serious adverse events (SAEs)

Study NEOSPHERE

During the neoadjuvant period, the incidence of SAEs was broadly comparable in the T+D arm, Ptz+T+D arm and the Ptz+D arm (15-20 SAEs per arm in 10%-17% of patients), and lowest in the Ptz+T arm (4 SAEs, 4% of patients). The most frequently reported SAEs in the T+D arm, Ptz+T+D arm and the Ptz+D arm were neutropenia and febrile neutropenia; however SAEs occurred across multiple body systems, with no marked difference in incidence between any of these arms. One patient in the Ptz+T+D arm experienced an SAE of fulminant hepatitis that was fatal. One patient in the Ptz+T arm experienced an SAE of congestive cardiac failure in the neoadjuvant.

During the adjuvant period, the incidence of SAEs was highest in the Ptz+T arm (18.1%). Most of the SAEs in the Ptz+T arm were events known to be associated with docetaxel (neutropenia, febrile neutropenia and neutropenic infection); therefore, the higher incidence in the Ptz+T arm was likely due to the administration of docetaxel during the adjuvant period in this arm (all other arms received docetaxel in the neoadjuvant period only). SAEs that occurred in > 1 patient in any treatment arm included febrile neutropenia, neutropenia, pyrexia and LVD.

Following completion of adjuvant chemotherapy, a total of 10 patients experienced SAEs during adjuvant trastuzumab (4 [3.9%] in the Ptz+T+D arm, 5 [5.3%] in the Ptz+T arm and 1 [1.1%] in the Ptz+D arm), all of which resolved with no sequelae.

During the post-treatment follow-up period, 1 patient in the Ptz+D arm experienced an SAE of myeloproliferative disorder. The event was considered possibly related to study treatment (epirubicin and cyclophosphamide), and remained unresolved at the time of the clinical cutoff date.

Study TRYPHAENA

The incidence of SAEs during the neoadjuvant period was highest in the Ptz+TCH arm (36%), followed by the Ptz+T+FEC/Ptz+T+D arm (28%) and then the FEC/Ptz+T+D arm (20%). The most common SAE was febrile neutropenia, and this was lower in the FEC/Ptz+T+D arm (5%) than in the Ptz+T+FEC/Ptz+T+D arm and Ptz+TCH arm (14% and 15%, respectively). Diarrhea SAEs were reported in 1%, 4% and 5% of patients, and neutropenia in 3%, 4% and 1% of patients, in the Ptz+T+FEC/Ptz+T+D, FEC/Ptz+T+D and Ptz+TCH arms, respectively. All other events occurred in only one or two patients in any arm.

A total of 5 patients experienced cardiac disorder SAEs. These included: 3 reports of LVD (1 in the Ptz+T+FEC/Ptz+T+D arm; 2 in the FEC/Ptz+T+D arm) and one report each of cardiovascular disorder and conduction disorder in the Ptz+TCH arm.

In the adjuvant period, 5 patients in the Ptz+T+FEC/Ptz+T+D arm (7.4%), 4 patients in the FEC/Ptz+T+D arm (6.2%) and 6 patients (9.0%) in the Ptz+TCH arm experienced at least one SAE. Apart from pneumonia, which occurred in two patients in the Ptz+T+FEC/Ptz+T+D arm, all events occurred in single patients. There was one cardiac disorder: symptomatic LVSD NYHA Class I reported one patient in the Ptz+TCH arm.

Two patients, both in the FEC/Ptz+T+D arm, experienced SAEs assessed as treatment-related in the post-treatment follow-up period at the time of the clinical cutoff of 22 July 2013. One patient experienced NYHA Class II symptomatic LVSD (NCI-CTCAE Grade 3) which later improved and one patient, who received docetaxel in the post-treatment follow-up period, experienced Grade 4 neutropenia (this event lasted 3 days, and had resolved at the last assessment).

Study CLEOPATRA

The incidence of SAEs was higher in the Ptz+T+D arm (36.3%) than in the Pla+T+D arm (29.0%). Serious adverse events in the SOC, Blood and Lymphatic System Disorders were the most frequently reported SAEs in both treatment arms; these occurred more frequently in the Ptz+T+D arm than in the Pla+T+D arm (15.9% vs. 10.6%, respectively). The difference between the two treatment arms was mainly due to a higher incidence of febrile neutropenia in the Ptz+T+D arm (11.3% of patients) compared with the Pla+T+D arm (5.1% of patients).

The next most frequently reported SOC was Infections and Infestations. Events in this class were also more common in the Ptz+T+D arm (11.8% of patients) than in the Pla+T+D arm (8.6% of patients). However, no single event accounted for the difference in incidence between the two arms.

Although the incidence of Gastrointestinal Disorder SAEs was balanced between the two treatment arms, SAEs of diarrhea were more common in the Ptz+T+D arm (3.2% of patients) than in the Pla+T+D arm (1.3% of patients). General Disorders and Administration Site SAEs were more frequent in the Ptz+T+D arm (3.4% of patients) compared with the Pla+T+D arm (2.3% of patients). Respiratory, Thoracic, and Mediastinal Disorders were also more frequent in the Ptz+T+D arm (3.2% of patients) compared with the Pla+T+D arm (2.3% of patients). However, the difference between the arms was small (< 2.0%) in both cases, and no clear difference in any individual event was observed. The proportion of patients who experienced Cardiac Disorder SAEs was higher in the Pla+T+D arm (3.5% of patients) than in the Ptz+T+D arm (1.7% of patients).

Laboratory findings

Study NEOSPHERE

Overall, the most common laboratory abnormalities were decreased neutrophil, total WBC and lymphocytes. Grade 3-4 neutropenia was more common in Arms A (T+D) and C (Ptz+T), while occurring with a slightly lower frequency in Arm B (Ptz+T+D). The incidence of NCI-CTCAE v.3 Grade 3-4 neutropenia was 74.5% in patients treated with neoadjuvant Perjeta, trastuzumab and docetaxel compared with 84.5% in patients treated with trastuzumab and docetaxel, including 50.9% and 60.2% Grade 4 neutropenia, respectively (see SmPC section 4.8). The addition of pertuzumab to trastuzumab in the neoadjuvant period did not lead to an unexpected increase in laboratory abnormalities.

With regard to biochemistry (ASAT, LDH, ALP, ALAT, bilirubin and creatinine) the pattern in shifts was comparable between the arms that included docetaxel. Most of the shifts were Grade 1-2. There were some shifts in calcium levels from Grade 0 to Grade 4 (mostly decreased calcium) and increased uric acid, which are some of the indicators for increased cell turnover. This could cause acute renal failure, but there was no indication of that, when looking at the creatinine levels or the overall AE profile.

There was one patient who fulfilled Hy's law but no firm conclusion can be drawn.

Study TRYPHAENA

The most common AEs were decreased neutrophil and total WBC counts. Grade 3-4 neutropenia was most frequently observed in Arm A (Ptz+T+FEC/Ptz+T+D). The incidence of NCI-CTCAE v.3 Grade 3-4 neutropenia was 85.3% in patients treated with neoadjuvant Perjeta + TCH and 77.0% in patients treated with neoadjuvant Perjeta, trastuzumab and docetaxel following FEC, including 66.7% and 59.5% Grade 4 neutropenia, respectively.

Balanced shift were observed across treatment arms with regard to the biochemistry data. Also increased uric acid levels were observed, indicating increased cell turnover.

Vital signs

There were no unexpected findings in the two neoadjuvant trials.

Safety in special populations

Intrinsic factors

Age

The number of patients over 65 years in the two neoadjuvant trials was too small to draw any meaningful conclusion.

Race

NEOSPHERE

The only reasonable comparison was between white and Asian patients. Asian patients had (independent of treatment arm) a higher incidence of Grade ≥ 3 AEs, SAEs, AEs leading to dose interruption/modification, leukopenia, diarrhoea, rash and mucositis.

TRYPHAENA

Asian patients had also in this study a higher incidence of Grade ≥ 3 AEs, leukopenia, diarrhea and rash. The most apparent difference is seen leukopenia; 87.5% (Asian) vs. 54.4% (white).

Extrinsic factors

Region

NEOSPHERE: Since the only reasonable comparison was between Europe and Asia, the same AE pattern as in the assessment of AEs based on "race" is observed.

TRYPHAENA: There were too few non-Europeans to make any reasonable comparison between different regions.

Discontinuation due to adverse events

Study NEOSPHERE

During the neoadjuvant period, 7 patients (0 in the T+D arm, 2 [1.9%] in Ptz+T+D arm, 3 [2.8%] in the Ptz+T arm and 2 [2.1%] in the Ptz+D arm) discontinued from any study treatment because of AEs. Two patients discontinued docetaxel due to drug hypersensitivity (one in the Ptz+T+D arm and one in the Ptz+T arm). In the Ptz+T arm, one patient withdrew from all medication due to CHF and one patient withdrew from all medication due to pregnancy. In the Ptz+D arm, one withdrew from pertuzumab and docetaxel due to neutropenia, and one patient who discontinued due to ulcerative colitis, had received all cycles of pertuzumab and all 21 cycles of trastuzumab but had not started any cycles of FEC. All AEs leading to treatment discontinuation were considered possibly related to treatment, with the exception of the ulcerative colitis, which was assessed as unrelated by the investigators.

During the adjuvant period, a total of 10 patients (0 in the T+D arm, 3 in the Ptz+T+D arm, 5 in the Ptz+T arm and 2 in the Ptz+D arm) discontinued from any study treatment because of AEs during the adjuvant period. The AEs leading to discontinuation of study medication included: LVD (2 patients) and abdominal strangulated hernia in the Ptz+T+D arm; asthenia, chest discomfort, drug hypersensitivity (2 patients) and septic shock in the Ptz+T arm; and LVD (2 patients) in the Ptz+T arm. Four patients (2 in the Ptz+T+D arm and 2 in the Ptz+D arm) discontinued from a study treatment during adjuvant trastuzumab treatment after adjuvant chemotherapy.

Study TRYPHAENA

Both in the neoadjuvant and adjuvant period very few patients discontinued treatment (4 patients [5.6%], 5 patients [6.7%] and 6 patients [7.9%] in the Ptz+T+FEC/Ptz+T+D, FEC/Ptz+T+D and Ptz+TCH arms, respectively in the neadjuvant period). Pertuzumab seemed to be well-tolerated irrespective of backbone chemotherapy (antracycline vs. non-antracycline).

Adverse Events That Led to Dose Modification or Interruption

Study NEOSPHERE

During the neoadjuvant period, the number of patients who experienced an AE that required treatment interruption or modification was highest in the Ptz+D arm (43.6%) and lowest in the Ptz+T arm (14.8%) and was comparable between the T+D arm and Ptz+T+D arm (34.6% and 32.7% respectively). The most frequently reported AEs (in at least 5 patients in each arm) requiring dose modification were: neutropenia (in 9.3%, 5.6%, 0.9% and 16% of patients in the T+D, Ptz+T+D, Ptz+T and Ptz+D arms, respectively); infusion-associated reaction (in 4.7%, 3.7%, 2.8% and 4.3% of patients in the T+D, Ptz+T+D, Ptz+T and Ptz+D arms, respectively); diarrhea (in 0.9%, 7.5%, 0% and 4.3% of patients in the T+D, Ptz+T+D, Ptz+T, and Ptz+D arms, respectively); febrile neutropenia (in 6.5%, 3.7%, 0% and 4.3% of patients in the T+D, Ptz+T+D, Ptz+T and Ptz+D arms, respectively); and drug hypersensitivity (in 0.9%, 1.9%, 4.6% and 4.3% of patients in the T+D, Ptz+T+D, Ptz+T and Ptz+D arms, respectively).

Three patients in the Ptz+T+D arm experienced LVD leading to dose modification during the neoadjuvant period. All 3 events were assessed as possibly related to study treatment, and resolved without sequelae.

During the adjuvant period, the incidence of AEs leading to dose interruption or modification of any study treatment was slightly higher in the Ptz+T arm compared with the other treatment arms (32.0% in the T+D arm, 34.3% in the Ptz+T+D arm, 43.6% in the Ptz+T arm and 37.5% in the Ptz+D arm), as would be expected since patients in this treatment arm received 3 cycles of docetaxel (in addition to 3 cycles of FEC) during the adjuvant period (all other arms received docetaxel in the neoadjuvant period only). The most frequently reported AEs leading to dose interruption or modification were similar to those reported in the neoadjuvant period.

Study TRYPHAENA

During the neoadjuvant period, a total of 36.1% patients in the Ptz+T+FEC/Ptz+T+D arm, 29.3% of patients in the FEC/Ptz+T+D arm, and 50.0% of patients in the Ptz+TCH arm experienced an AE that required treatment modification or interruption in the neoadjuvant period. Dose modifications were common in all treatment arms, and were primarily performed in order to manage Blood and Lymphatic System Disorders. Neutropenia was the single most reported event leading to dose modification (between 14%-15% of patients). In the Ptz+TCH arm, anemia (21% of patients) and thrombocytopenia (16%) were also common AEs leading to dose modification. Investigations (for laboratory abnormalities) also led to dose modification in 11% of patients in the Ptz+TCH arm.

Compared with the neoadjuvant period, fewer patients experienced AEs leading to dose modification (8 patients [11.8%] in the Ptz+T+FEC/Ptz+T+D arm, 11 patients [16.9%] in the FEC/Ptz+T+D arm and 4 patients [6.0%] in the Ptz+TCH arm) in the adjuvant period. This is to be expected since most patients received only adjuvant trastuzumab during this period and dose reductions were not permitted.

Study CLEOPATRA

As of the clinical data cutoff (14 May 2012), the incidence of AEs leading to interruption or dose modification of any of the three study medications was higher in the Ptz+T+D arm (252 patients [61.8%]) compared with the Pla+T+D arm (215 patients [54.3%]). The difference in overall incidence between treatment arms was due to a range of events in different body systems. There were more AEs of febrile neutropenia (20 patients in the Pla+T+D arm [5.1%] vs. 31 patients in the Ptz+T+D arm [7.6%]), hypersensitivity (9 patients Pla+T+D [2.3%] vs. 18 patients Ptz+T+D [4.4%]) and diarrhea (7 patients Pla+T+D [1.8%] vs. 23 patients Ptz+T+D [5.6%]) that led to dose modification in the Ptz+T+D arm compared with the Pla+T+D arm. Conversely, there were more AEs of LVD leading to interruption or dose modification in the Pla+T+D arm (11 patients [2.8%]) compared with the Ptz+T+D arm (5 patients [1.2%]).

Adverse drug reactions

The integrated safety database has been updated to include data from the TRYPHAENA study and updated data from the NEOSPHERE and CLEOPATRA studies. The integrated safety database now contains data for 1631 patients exposed to pertuzumab in 15 studies. Updated analyses based on these pooled data were provided and results of these analyses were consistent with the previous pooled analyses and with the NEOSPHERE, TRYPHAENA and CLEOPATRA safety data reported in above, with no new or unexpected findings. No new ADRs have been identified from the NEOSPHERE or TRYPHAENA studies. Pooled data from the overall treatment period in CLEOPATRA (data cutoff 11 February 2014; median number of cycles of Perjeta was 24); and from the neoadjuvant treatment period in NEOSPHERE (median number of cycles of Perjeta was 4, across all treatment arms) and TRYPHAENA (median number of cycles of Perjeta was 3 – 6 across treatment arms) have been provided. On this basis, the frequencies of the following ADRs have been revised from very common to common: Peripheral sensory neuropathy, Dizziness, Lacrimation increased, Dyspnoea, Pruritus and Dry skin (see SmPC section 4.8).

Post marketing experience

Pertuzumab (Perjeta) in combination with trastuzumab and docetaxel for the first-line treatment of patients with HER2-positive MBC was first approved in the US on 08 June 2012. Subsequently, it was approved in the EU and many other countries for the treatment of MBC, and in the US, Chile and Peru for the neoadjuvant treatment of patients with earlier stages of disease.

This section summarizes the post-marketing experience with pertuzumab on the basis of safety data contained in the second Periodic Benefit-Risk Evaluation Report (PBRER), which covers the reporting interval 8 June 2013 to 7 December 2013. The estimated total cumulative exposure to pertuzumab via company-sponsored or development partner-sponsored studies or through commercially available product since the Development International Birth Date (DIBD; 11 September 2001) until the Data Lock Point (DLP) for the second PBRER (7 December 2013) was 17,077 patients worldwide, including approximately 11,346 patients exposed to commercially obtained drug.

Table 104 Cumulative Pertuzumab Exposure from Marketing Experience

Indication	Sex			Age (years)				Region			
	M	F	Unk	2 to ≤ 16	> 16 to ≤ 65	> 65	Unk	Europe	USA	RoW	Japan
MBC	50	6,187	4,588	0	3,680	2,557	4,588	2,392	6,237	676	1,520
EBC	4	517	0	0	391	130	0	0	521	0	0
Total	54	6,704	4,588	0	4,071	2,687	4,588	2,392	6,758	676	1,520
Grand Total	11,346			11,346				11,346			

EBC = early breast cancer; F = female; M = male; MBC = metastatic breast cancer; RoW = rest of world; Unk = unknown

Table 106 Cumulative Summary Tabulations of Serious Adverse Reactions from Post-Marketing Sources*

System Organ Class	Spontaneous, including regulatory authority and literature	Non-interventional post-marketing study
	Serious Cumulative	Serious Cumulative
Infections and infestations	13	15
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	15	29
Blood and lymphatic system disorders	23	33
Immune system disorders	11	4
Endocrine disorders	0	0
Metabolism and nutrition disorders	5	11
Psychiatric disorders	2	0
Nervous system disorders	15	18
Eye disorders	3	1
Ear and labyrinth disorders	0	0
Cardiac disorders	19	23
Vascular disorders	9	1
Respiratory, thoracic and mediastinal disorders	45	19
Gastrointestinal disorders	67	28
Hepatobiliary disorders	5	8
Skin and subcutaneous tissue disorders	22	4
Musculoskeletal and connective tissue disorders	4	6
Renal and urinary disorders	3	5
Pregnancy, puerperium and perinatal conditions	0	0
Reproductive system and breast disorders	0	0
General disorders and administration site conditions	59	78
Investigations	19	10
Injury, poisoning and procedural complications	13	8
Surgical and medical procedures	0	3
Social circumstances	1	0
TOTAL	**353**	**304**

Table is derived from Appendix 3 of PBRER No. 1053870 (08 June 2013 to 07 December 2013).

* Non-interventional studies and spontaneous ICSRs (i.e., reports from healthcare professionals, consumers, regulatory authorities, and scientific literature).

Cumulative data covering the period from 08 June 2012 (IBD) to 07 December 2013.

2.5.4. Discussion on clinical safety

The safety of Perjeta has been evaluated in more than 1,600 patients in the randomized trials CLEOPATRA (n=808), NEOSPHERE (n=417) and TRYPHAENA (n=225) and in phase I and II trials conducted in patients with various malignancies and predominantly treated with Perjeta in combination with other antineoplastic agents.

The duration of the exposure of patients in the two neoadjuvant studies is limited, while patients in the CLEOPATRA study have a much higher exposure. Although the patient population enrolled in the CLEOPATRA study had more advanced disease than patients in the NEOSPHERE and TRYPHAENA studies, protocol entry criteria were otherwise very similar between the three studies. Importantly, most patients in the CLEOPATRA study received much more treatment with pertuzumab in combination with trastuzumab and docetaxel than would be given in the neoadjuvant setting. Thus, the CLEOPATRA study is more likely to have revealed any safety issues with this combination regimen than the two neoadjuvant studies, in which treatment duration was relatively short. With a median time on study (including follow-up) greater than two years for patients in the CLEOPATRA study, there has also been sufficient follow-up for any delayed and/or cumulative toxicity to have emerged.

There is no safety data available on the continued use of Perjeta for more than 6 cycles in the neoadjuvant setting (see SmPC section 4.8).

Overall, the safety of Perjeta in Phase I and II studies was generally consistent with that observed in the CLEOPATRA, NEOSPHERE and TRYPHAENA trials, although the incidence and most common adverse drug reactions (ADRs) varied depending on whether perjeta was administered as monotherapy or with concomitant anti-neoplastic agents (see SmPC section 4.8).

In general, in all three studies, the most common adverse events were leukopenia, rash and diarrhoea.

In the NEOSPHERE study, it is observed that AEs are more likely in Arm B (Ptz+T+D). These AEs were mostly related to gastrointestinal, skin and subcutaneous, blood and lymphatic and musculoskeletal disorders. The interesting comparison is between Arm A (T+D) and Arm B (Ptz+T+D), and the only major difference was seen in gastrointestinal disorders, 61.7% vs. 79.4%.

The most frequent AEs reported in Study NEOSPHERE were neutropenia, diarrhoea, alopecia and rash. In Arm C (T+Ptz) there were only two cases of alopecia and neutropenia. When comparing Arm A (T+D) with Arm D (Ptz+D) almost an identical safety profile was observed, except for diarrhoea, which was more common in Arm D. Thus, pertuzumab by itself may lead to a higher risk of diarrhoea, which is manageable in the clinical setting.

Overall, there were no unacceptable additional toxicities by adding pertuzumab to trastuzumab in the neoadjuvant setting. The safety profile was slightly altered in the adjuvant setting compared to the neoadjuvant setting. Nausea, neutropenia, vomiting, fatigue and diarrhoea were the most frequent AEs. Alopecia was almost absent in Arm A (T+D), B (Ptz+T+D) and D (Ptz+D), while 59.6% of the patients in Arm C (T+Ptz) experienced it. The safety profile of Arm B (Ptz+T+D) is considered manageable.

The majority of Grade ≥ 3 AEs occurred in the blood and lymphatic system, with more AEs in Arms A and D in the NEOSPHERE study, but the risk of febrile neutropenia seems to be similar in all treatment arms. Neutropenia is a well-known and well-characterised Adverse Events of Special Interest (AESI) already addressed in the SmPC.

In the TRYPHAENA study, the most frequent AEs in the neoadjuvant setting in Arm A (Ptz+T+FEC/Ptz+T+D) and B (FEC/Ptz+T+D) were similar to the safety profile in adjuvant setting in

the NEOSPHERE study, which is not surprising since FEC was administered to the patients. In Arm C (Ptz+TCH), where patients received the non-anthracycline regimen (docetaxel+carboplatin+trastuzumab +pertuzumab) patients experienced more myelotoxic related AEs (anaemia, neutropenia, thrombocytopenia, etc.), due to the toxic effects of carboplatin and docetaxel on the bone marrow. However, all these AEs are clinically manageable and do not lead to any major concerns.

All patients received trastuzumab up to 1 year in the adjuvant setting. AEs occurred less frequently in the non-anthracycline arm (Arm C). There were slight differences between Arm A (Ptz+T+FEC/Ptz+T+D) and B (FEC/Ptz+T+D), except for a relevant difference in upper respiratory tract infections (2 (2.9%) vs. 8 (12.3%). However, all events were mild to moderate and they all resolved.

Overall, there seemed to be fewer Grade ≥ 3 AEs in Arm B (FEC/Ptz+T+D) in the TRYPHAENA study, but the incidence of AEs was more or less comparable. The predominant AEs were within the blood and lymphatic system. There were slightly more Grade 4 AEs in Arm C (Ptz+TCH), mostly in the "blood and lymphatic system disorders" SOC with predominantly neutropenia. This is a well-known risk of chemotherapy and it is clinically manageable. There were no Grade 5 AEs.

In the CLEOPATRA study, the AE profile of Ptz+T+D in the metastatic breast cancer (MBC) resembled the profile of Arm B (Ptz+T+D) in the neoadjuvant setting in early breast cancer. However, patients in the MBC setting received 6 cycles of docetaxel, while patients in the NEOSPHERE study received only 4 cycles, which may explain some of the differences. Patients in the MBC setting were also heavily pre-treated compared to the treatment naïve patients in the neoadjuvant setting. The only major difference was diarrhoea, which occurred more often in the MBC setting. Overall, the safety profile of pertuzumab is comparable between the neoadjuvant and MBC setting.

With regard to AESI, there were slightly more cardiac disorders in Arm B (Ptz+T+D) in the NEOSPHERE study. Overall, the incidence of LVD was higher in the pertuzumab–treated groups than in those who did not receive pertuzumab in the NEOSPHERE study (see SmPC sections 4.4 and 4.8). Although there were more cases of LVD in the Ptz+T+D arm, these were only Grade 3, asymptomatic and in some cases seen in patients with cardiac risk factors. An increased incidence of LVEF declines was also observed in patients treated with pertuzumab in combination with trastuzumab and docetaxel. LVEF recovered to ≥50% in all patients (see SmPC sections 4.4 and 4.8). LVEF should be assessed prior to initiation of pertuzumab and during treatment with Perjeta (every 3 cycles in the metastatic setting and every 2 cycles in the neoadjuvant setting) to ensure that LVEF is within the institution's normal limits (see SmPC section 4.4).

The primary safety endpoint in the TRYPHAENA study concerned cardiac safety. There were only very few cases of symptomatic LVSD, and there was no sign of any difference between the treatment arms. There were slightly more patients with LVEF decline in Arm B (FEC/Ptz+T+D) and C (Ptz+TCH). One patient had a prior history of myocardial ischemia, which may have contributed to the LVSD during administration of pertuzumab in the neoadjuvant period. There were too few events to draw any conclusions. Very few patients discontinued treatment due to cardiac events.

A direct comparison may not be appropriate since the patient populations differ, etc., but nonetheless the frequency of LVSD, Grade ≥ 3 LVSD, LVEF decline and CHF, seemed to be comparable between the Ptz+T+D arm in the NEOSPHERE study and the experimental arm Ptz+T+D in the CLEOPATRA study, with only slight differences. Thus, the use of pertuzumab in the neoadjuvant setting did not lead to excess of cardiac toxicity. This is also supported by results from the TRYPHAENA study.

Left ventricular dysfunction is a well-known risk that is clearly described in the SmPC for the use of pertuzumab in the metastatic setting, and is clinically manageable. Nevertheless, the long-term cardiac safety of pertuzumab in the neoadjuvant phase is considered incompletely characterized at present. The study APHINITY, BERENICE and the final analysis of TRYPHAENA should provide further evidence with regard to this safety concern (see RMP).

With regard to the remaining AESI, the incidence of infusion-related reactions was considerable higher in the NEOSPHERE and TRYPHAENA compared to the CLEOPATRA study. However, Infusion reactions were consistent with those observed in CLEOPATRA at the cycles when Perjeta was given on the same day as trastuzumab and docetaxel, with a majority of reactions being mild or moderate (see SmPC section 4.8).

Rash rates were higher in pertuzumab containing arms in the NEOSPHERE study and an additional effect was noted with Docetaxel. In the TRYPHAENA study, Ptz and TCH had the worst effect on rash rates (see SmPC section 4.8). Regarding leukopenia, a similar rate of leukopenia events was reported in chemotherapy containing regimens with a lower incidence in the Ptz+T+D arm in the NEOSPHERE study. A slightly higher incidence of febrile neutropenia was observed in the Ptz+T+D arm however very few infections were reported indicating that the episodes were clinically manageable. In the TRYPHAENA study a lower rate of leukopenic events and in particular of febrile neutropenia was reported in the FEC/Ptz+T+D arm when compared with the same regimen given longer or to TCH (see SmPC section 4.8).

Diarrhoea was confirmed as one of the most common AE reported in Ptz containing regimens. In particular the rate was higher in the Ptz+T+D arm of the NEOSPHERE study and in the TCH+Ptz arm of the TRYPHAENA study. However, only a minority of episodes were of severe grade and none lead to treatment discontinuation (see SmPC section 4.8).

Overall, there is no indication of any excess cases of diarrhoea, rash, mucositis, interstitial lung disease, hepatic disorders, VTEs, neutropenia or febrile neutropenia by adding pertuzumab to trastuzumab in the neoadjuvant setting.

In the NEOSPHERE study, most SAEs occurred in Arm A (T+D) and D (Ptz+D) in the neoadjuvant period. Most frequent SAEs in all treatment arms were neutropenia and febrile neutropenia. The pattern of SAE was comparable to the experimental arm in the CLEOPATRA study. In the neoadjuvant period the TRYPHAENA study, most SAEs occurred in the non-anthracycline arm (Arm C (Ptz+TCH)). Across all three arms, diarrhoea, neutropenia and gastrointestinal disorders occurred most frequently. All are reflected in the SmPC (see SmPC section 4.8). Very few SAEs were observed in the adjuvant and post-treatment follow-up period in the TRYPHAENA study.

Overall, the addition of pertuzumab to trastuzumab in the neoadjuvant setting did not lead to any unexpected safety findings in the NEOSPHERE study. This is supported by the results of the TRYPHAENA study and the CLEOPATRA study. The TRYPHAENA study also provided evidence with regard to cardiac toxicity. There is currently no indication of any concerning differences in tolerability by adding pertuzumab + trastuzumab to anthracyclines or carboplatin in the neoadjuvant period.

However, cardiac risk should be carefully considered and balanced against the medical need of the individual patient before use of Perjeta with an anthracycline. There are limited safety data available from the TRYPHAENA study concerning sequential or concomitant administration of Perjeta with epirubicin, as part of the FEC regimen (see sections 4.8 and 5.1). There are no safety data available concerning use of Perjeta with doxorubicin.

Based on the pharmacological actions of pertuzumab and anthracyclines an increased risk of cardiac toxicity might be expected from concomitant use of these agents compared with sequential, although not seen in the TRYPHAENA study. In this study, only chemotherapy-naive subjects, not receiving additional chemotherapy after surgery, were treated with low cumulative dose of epirubicin, i.e. up to 300 mg/m^2 (see SmPC section 4.4).

2.5.5. Conclusions on clinical safety

Overall, the observed adverse events are well-characterised, clinically manageable and adequately reflected in the SmPC. However, long-term cardiac toxicity is incompletely characterized at present and requires follow-up. Thus, the following post-authorisation safety study has been included as condition in Annex II:

Post-authorisation safety study (PASS): In order to evaluate cardiac safety and provide further efficacy data in the neoadjuvant setting, the MAH should submit the results of study WO29217 (BERENICE), a multicentre, multinational, Phase II study to evaluate pertuzumab in combination with trastuzumab and standard neoadjuvant anthracycline-based chemotherapy in patients with HER2-positive, locally advanced, inflammatory, or early-stage breast cancer.	May 2017

In addition, safety data from the study APHINITY and the final analysis of TRYPHAENA are expected to provide further evidence with regard to this safety concern as reflected in the Risk Management Plan.

2.5.6. PSUR cycle

The PSUR cycle remains unchanged.

The annex II related to the PSUR, refers to the EURD list which remains unchanged.

2.6. Risk management plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 3.3 could be acceptable if the applicant implements the changes to the RMP as described in the PRAC endorsed PRAC Rapporteur assessment report.

The CHMP endorsed this advice with the following changes: the results from the BO25126 (APHINITY) and WO29217 (BERENICE) studies should be submitted as an obligation of marketing authorization.

The applicant implemented the changes in the RMP as requested by PRAC and CHMP.

The CHMP endorsed the Risk Management Plan version 5.1 with the following content (new text marked as underlined, deletions marked as strikethrough):

Safety concerns

Important Identified Risks	• Exacerbation of chemotherapy/docetaxel-associated neutropenia • Infusion-related reactions, Hypersensitivity reactions/anaphylaxis • Congestive heart failure • Mucositis • Grade ≥ 3 Diarrhoea • Interstitial lung disease
Important Potential Risks	• Oligohydramnios[1]
Missing Information	• Risk in patients aged 75 years or older • Risk in pregnant women • Risk in lactating women • Risk in fertility in humans • Risk in male breast cancer patients • Risk in patients with cardiovascular impairment • Risk in patients with hepatic impairment • Risk in patients with severe renal impairment • Risk of lack of efficacy due to immunogenicity

[1]Oligohydramnios has not been reported in patients treated with pertuzumab but occurred in cynomolgus monkeys administered pertuzumab and in pregnant women treated with trastuzumab. Due to age, prior adjuvant treatment, concurrent chemotherapy, the advanced stage of disease and poor prognosis in the patient population, the MAH assesses the likelihood of pregnancies to be low.

Pharmacovigilance plan

Study / activity Type, title and category (1-3)	**Objectives**	**Safety concerns addressed**	**Status**	**Date for submission of interim or final reports**
BO22280 (TRYPHAENA) 3	After completion of trastuzumab LVEF to be performed every 6 months for 2 years then annually, for a further 2 years.	Congestive heart failure	study on-going	2014 (update) 2016 (final)

Study / activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status	Date for submission of interim or final reports
~~BO25126 (APHINITY) 3~~	~~incidence of CHF and/or decrease in LVEF including long-term cardiac monitoring (ECG, LVEF, signs and symptoms) for up to 10 years of follow-up~~	~~Congestive heart failure~~	~~study on-going~~	~~2017 (interim)~~ ~~2023 (final)~~
MO22324 (PHEREXA) 1	Investigate combination of pertuzumab with trastuzumab and capecitabine (known for a potential cardiac ischemic effect)	Congestive heart failure	study on-going	December 2015
MO28047 (PERUSE) 1	Independent safety monitoring board and will provide further information and characterisation of cardiac risk in patients receiving pertuzumab.	Congestive heart failure	study on-going	March 2019 ~~2016~~
MotHER 3	to collect pregnancy outcomes following exposure to pertuzumab	oligohydramnios	approved	2022
Global Enhanced PV Pregnancy Program 1	to collect additional information on women exposed to pertuzumab plus trastuzumab during pregnancy or within six months prior to	potential risk of oligohydramnios or other fetal/infant abnormalities	CHMP approved	A cumulative and interval summary of all pertuzumab-exposed pregnancy cases and their outcomes, will be presented in each

Study / activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status	Date for submission of interim or final reports
	conception and to follow-up on the infant after birth, and at 3, 6 and 12 months of life in order to better assess and describe potential adverse pregnancy complications			PSUR for 10 years ~~Not applicable~~
WO20698 / CLEOPATRA 3	long-term follow up of cardiac events	all safety concerns	on-going	2014 (update CSR) ~~(final)~~
WO29217 BERENICE 1	to evaluate the cardiac safety of neoadjuvant treatment with pertuzumab in combination with trastuzumab and anthracycline/ taxane-based chemotherapy regimens	Congestive heart failure	on-going	May 2017

Risk minimisation measures

Safety Concern	Routine Risk Minimization Activities	Additional risk minimization measures
Important identified risk		
Exacerbation of chemotherapy/ docetaxel - associated neutropenia	Section 4.8 of the SmPC	None proposed
Infusion-related reactions / Hypersensitivity reactions/anaphylaxis	Section 4.4 of the SmPC	None proposed
Congestive heart failure	Sections 4.2 and 4.4 of the SmPC	None proposed

Safety Concern	Routine Risk Minimization Activities	Additional risk minimization measures
Mucositis	Sections 4.4 and 4.8 of the SmPC	None proposed
Grade ≥ 3 Diarrhea	Section 4.8 of the SmPC	None proposed
Interstitial lung disease	Section 4.8 of the SmPC	None proposed
Important potential risk		
Oligohydramnios	Section 4.6 of the SmPC	None proposed
Missing Information		
Risk in patients aged 75 years or older	Section 4.2 of the SmPC	None proposed
Risk in pregnant women	Section 4.6 of the SmPC	None proposed
Risk in lactating women	Section 4.6 of the SmPC	None proposed
Risk in fertility in humans	Section 4.6 of the SmPC	None proposed
Risk in male breast cancer patients	Section 5.3 of the SmPC ~~Section 4.6 of the SmPC~~	None proposed
Risk in patients with cardiovascular impairment	Section 4.2 and 4.4 of the SmPC	None proposed
Risk in patients with hepatic impairment	Section 4.2 of the SmPC	None proposed
Risk in patients with renal impairment	Section 4.2 of the SmPC	None proposed
Risk of lack of efficacy due to immunogenicity	Section 5.1 of the SmPC	None proposed

2.7. Update of the Product information

As a consequence of this new indication, changes are proposed to sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2 of the SmPC. The Package Leaflet has been updated accordingly.

In addition, the MAH took the opportunity to make a correction in sections 2 and 6.6 of the SmPC regarding the dose contained in 1 ml of solution after dilution. 14 ml of Perjeta concentrate should be withdrawn from the vial and diluted into a 250 ml PVC or non-PVC polyolefin infusion bag of sodium

chloride 9 mg/ml (0.9%) solution for infusion. After dilution, one ml of solution should contain approximately 3.02 mg of pertuzumab (840 mg/278 ml) for the initial dose where two vials are required and approximately 1.59 mg of pertuzumab (420 mg/264 ml) for the maintenance dose where one vial is required.

This change was accepted by the CHMP.

3. Benefit-Risk Balance

Benefits

Beneficial effects

The NEOSPHERE study showed a statistically significant and clinically relevant result with regard to pCR rate. The bpCR rate was 29% versus 45.8% in T+D arm and Ptz+T+D arm respectively. The tpCR (ypT0/is N0) rates showed the same pattern with a 17.8% difference in favour of the Ptz+T+D arm (39.3%) compared to the Ptz+T arm (21.5%).

These results are supported by the findings in the TRYPHAENA study, where pCR was a secondary endpoint. In this study, the reported pCR rates were 61.6%, 57.3%, 66.2% in the Ptz+T+FEC/Ptz+T+D arm, FEC/Ptz+T+F arm and Ptz+TCH arm respectively.

Supportive evidence of efficacy is provided by the CLEOPATRA study in the metastatic setting. In this study, the improvement in progression-free survival (PFS) in the pertuzumab arm was statistically significant [HR, 0.62; 95% confidence interval (CI), 0.51–0.75; p< 0.0001, log-rank test]. Moreover, a statistically significant improvement in OS of 15.7 months was observed in the pertuzumab+trastuzumab+docetaxel arm versus the placebo+trastuzumab+docetaxel arm with a HR of 0.68 (95% CI, 0.56-0.84; p=0.0002).

Uncertainty in the knowledge about the beneficial effects

The magnitude of the effect in terms of DFS/OS cannot be estimated from the observed pCR effect. However, the observed difference in tpCR rate of 17.8% between arm A (T+D) and B (Ptz+T+D) in the NEOSPHERE study is considered sufficiently large to be associated with a clinically meaningful improvement in long-term outcomes in the context of the totality of the data. Although not statistically significant, efficacy outcome data (DFS and OS) from the NEOSPHERE study showed a trend in favour of pertuzumab. This should also be seen in light of the survival benefit of adding pertuzumab to trastuzumab in the metastatic setting.

In both studies pCR rates and magnitude of improvement with pertuzumab were lower in the subgroup of patients with hormone-receptor-positive tumours compared to patients with hormone receptor-negative tumours. In the NEOSPHERE study, patients with hormone receptor-positive disease had lower bpCR rates (5.9% - 26%, across treatment arms [highest in Ptz+T+D arm]) than patients with hormone receptor-negative disease (27.3% - 63.2%, across treatment arms [highest in Ptz+T+D arm]). This observation is consistent with lower pCR rate observed in HR+ patients in the literature. However, a recently published meta-analyses (Cortazar et al. 2014, Lancet), which included individual patient data from approximately 12,000 patients, showed that there is a statistically significant and clinically relevant advantage in terms of long-term outcomes in patients with HER2+ disease, who achieve a pCR, irrespective of hormone receptor status. In addition, there solid evidence from the CLEOPATRA study for a statistically significant and clinically meaningful advantage of the effect of pertuzumab in HER2+ breast cancer in the metastatic setting, regardless of hormone receptor status. In this study, a Hazard Ratio for OS of 0.71 (0.51, 0.96) in patients with HR+ disease, compared with

0.61 (0.47, 0.81) in patients with HR-negative disease was observed. Thus, it is reasonable to expect that this will also the case in the neoadjuvant setting.

The APHINITY study will provide confirmatory efficacy data both in the overall population and in the HER2+/HR+ subpopulation (see Annex II conditions). In addition, study BERENICE will also provide valuable efficacy data in the neoadjuvant setting.

Risks

Unfavourable effects

In the neoadjuvant trial NEOSPHERE, the most common ADRs (≥ 50%) seen with Perjeta in combination with trastuzumab and docetaxel were alopecia and neutropenia. The most common NCI-CTCAE v.3 Grade 3-4 ADR (≥ 10%) was neutropenia.

In the TRYPHAENA study, when Perjeta was administered in combination with trastuzumab and FEC (5-fluorouracil, epirubicin, cyclophosphamide) for 3 cycles followed by 3 cycles of Perjeta, trastuzumab and docetaxel, the most common ADRs (≥50%) were neutropenia, diarrhoea and nausea. The most common NCI-CTCAE v.3 Grade 3-4 ADRs (≥10%) were neutropenia, febrile neutropenia and leucopenia. When Perjeta was administered in combination with trastuzumab and docetaxel for 3 cycles following 3 cycles of FEC (5-fluorouracil, epirubicin, cyclophosphamide), the most common ADRs (≥ 50%) were diarrhoea, nausea and alopecia. The most common NCI-CTCAE v.3 Grade 3-4 ADRs (≥ 10%) were neutropenia and leucopenia. Similarly, when Perjeta was administered in combination with TCH (docetaxel, carboplatin and trastuzumab) for 6 cycles, the most common ADRs (≥ 50%) were diarrhoea and alopecia. The most common NCI-CTCAE v.3 Grade 3-4 ADRs (≥ 10%) were neutropenia, febrile neutropenia, anaemia, leucopenia and diarrhoea.

In general, there were slightly more AEs in the Ptz+T+D arm of the NEOSPHERE study, which is expected. Comparing Arm A (T+D) with Arm D (Ptz+D) almost an identical safety profile was observed, except for diarrhoea, which was more common in Arm D. Thus, pertuzumab by itself seems to impose a higher risk of diarrhoea, which is manageable in the clinical setting.

In the NEOSPHERE study, the incidence of LVD was higher in the pertuzumab–treated groups than in those who did not receive pertuzumab. An increased incidence of LVEF declines was also observed in patients treated with pertuzumab in combination with trastuzumab and docetaxel. LVEF recovered to ≥ 50% in all patients.

In the NEOSPHERE study, SAEs occurred more frequently in Arms A (T+D) and D (Ptz+D) in the neoadjuvant period. Most frequent SAEs in all treatment arms were neutropenia and febrile neutropenia. The pattern of SAE was comparable to the experimental arm in the CLEOPATRA study. In the neoadjuvant period in the TRYPHAENA study, SAEs occurred more frequently in the non-anthracycline arm (Arm C). Across all three arms, diarrhoea, neutropenia and gastrointestinal disorders occurred most frequently. All are reflected in the SmPC. Very few SAEs were observed in the adjuvant and post-treatment follow-up period in the TRYPHAENA study.

Overall, there was no indication of any unexpected excess of cases of diarrhoea, rash, mucositis, interstitial lung disease, hepatic disorders, VTEs, neutropenia or febrile neutropenia by adding pertuzumab to trastuzumab in the neoadjuvant setting.

Uncertainty in the knowledge about the unfavourable effects

The safety of Perjeta administered for more than 6 cycles in the neoadjuvant setting has not been established (see SmPC section 4.8).

With regard to LVEF/LVSD, there were too few events to draw any conclusions. Very few patients discontinued treatment due to cardiac events. There are limited safety data available from the TRYPHAENA study concerning sequential as well as concomitant administration of Perjeta with epirubicin, as part of the FEC regimen and there are no safety data available to support use of doxorubicin with pertuzumab. Therefore, cardiac risk should be carefully considered and balanced against the medical need of the individual patient before use of pertuzumab with an anthracycline. Based on the pharmacological actions of pertuzumab and anthracyclines an increased risk of cardiac toxicity might be expected from concomitant compared with sequential use of these agents, although not seen in the TRYPHAENA study (see SmPC section 4.4 and 5.1).

Although the safety database in the claimed indication is considered sufficient for a characterization of the safety profile, longer follow-up and monitor of some AEs, including cardiac toxicity, is still considered necessary (see Annex II and RMP).

Patients older than 65 years are scarcely represented (see SmPC sections 4.2 and 5.1 and RMP).

Benefit-Risk Balance

Importance of favourable and unfavourable effects

Treatment effect measured as pCR in the overall patient population in the neoadjuvant setting is considered clinically relevant and likely to be associated with a benefit on long-term outcomes (DFS and OS). The final analysis from the APHINITY study (phase III) should permit confirmation of the clinical benefit of pertuzumab observed in the neoadjuvant setting from the NEOSPHERE and TRYPHAENA studies.

The safety profile does not differ significantly from that already observed in the metastatic setting, although an increase in a number of AEs has been observed in the neoadjuvant setting with the number of treatment cycles, including neutropenia, febrile neutropenia, and diarrhoea. Most of AEs are manageable in the clinical setting. Overall, the add-on changes in toxicity are acceptable. Long-term cardiac toxicity will be further characterised in the ongoing APHINITY and BERENICE studies (see Annex II and RMP).

Benefit-risk balance

Overall, based on the results from studies NEOSPHERE and TRYPHAENA and in the context of the totality of data, the robust biological rationale for the combination, compelling efficacy results from the metastatic setting, the acceptable safety profile, the reasonable likelihood that the observed treatment effect with pertuzumab is associated with a benefit in long-term outcome (DFS and OS), the benefit-risk balance of pertuzumab in combination with trastuzumab and chemotherapy for the neoadjuvant treatment of adult patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer at high risk of recurrence is positive.

Discussion on the Benefit-Risk Balance

Considering the greater medical need in patients at high risk of recurrence and the available efficacy data from the two neo-adjuvant studies, the CHMP considered the uncertainties with regard to safety can be accepted in patients who are at high risk of recurrence. Therefore, the CHMP considered that the neoadjuvant indication should be restricted to this high risk patient population. Locally advanced and inflammatory breast cancers are considered as high-risk irrespective of hormone receptor status in the neoadjuvant setting. In early stage breast cancer, tumour size, grade, hormone receptor status and lymph node metastases should be taken into account in the risk assessment (see SmPC section 5.1).

All available data make it sufficiently likely that pertuzumab in combination with trastuzumab will increase the pCR rate as add-on to chemotherapy regimens. Specifically, an increase in pCR rates has been shown when pertuzumab is added to T+D (39 % versus 22 %; NEOSPHERE Study). Standard practice guidelines recommend pertuzumab as part of treatment regimens including an anthracycline (e.g. epirubicin as in FEC) and a taxane (e.g. docetaxel) (NCCN guideline). When Perjeta was added to T+D+FEC or TCH based regimens in the TRYPHAENA study, pCR was 55-64%. Furthermore, the overall amount of evidence available to date, do not demonstrate a meaningful increase in cardiac toxicity. Acknowledging that a longer follow-up is needed to be further reassured, in this high-risk population, it is in the best interest of patients allowing the possibility to use pertuzumab not only in combination with docetaxel as backbone chemotherapy regimen but also with other chemotherapy regimens and at least with TCH (i.e. docetaxel, carboplatin and trastuzumab, Arm C of TRYPHAENA), which did not raise concerns with regard to cardiac toxicity. As a result the CHMP considers that the indication should not be restricted to combination with docetaxel as chemotherapy backbone only and recommended the use of perjeta in combination with trastuzumab and chemotherapy.

4. Recommendations

Final Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

Extension of indication to include the use of pertuzumab in combination with trastuzumab and chemotherapy for the neoadjuvant treatment of adult patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer at high risk of recurrence.

As a consequence, update of sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2 of the SmPC. In addition, the MAH took the opportunity to make a correction in sections 2 and 6.6 of the SmPC regarding the dose contained in 1 ml of solution after dilution.

The Package Leaflet is updated in accordance.

The requested variation proposed amendments to the SmPC, Annex II, and Package Leaflet.

This CHMP recommendation is subject to the following amended conditions:

Conditions and requirements of the marketing authorisation

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
MO22324 (PHEREXA) A multicenter randomized Phase III study to compare the combination of trastuzumab and capecitabine, with or without pertuzumab, in patients with HER2-positive metastatic breast cancer that have progressed after one line of trastuzumab-based therapy in the metastatic setting	December 2015
MO28047 (PERUSE) A multicenter, open-label, single-arm study of pertuzumab in combination with trastuzumab and a taxane in first line treatment of patients with HER2- positive advanced (metastatic or locally recurrent) breast cancer	March 2019
Post-authorisation efficacy study (PAES): In order to provide long-term efficacy data in terms of DFS and OS, the MAH should submit the results of study BO25126 (APHINITY), a randomized multicenter, double-blind, placebo-controlled comparison of chemotherapy plus trastuzumab plus placebo versus chemotherapy plus trastuzumab plus pertuzumab as adjuvant therapy in patients with operable HER2-positive primary breast cancer	May 2017
Post-authorisation safety study (PASS): In order to evaluate cardiac safety and provide further efficacy data in the neoadjuvant setting, the MAH should submit the results of study WO29217 (BERENICE), a multicentre, multinational, Phase II study to evaluate pertuzumab in combination with trastuzumab and standard neoadjuvant anthracycline-based chemotherapy in patients with HER2-positive, locally advanced, inflammatory, or early-stage breast cancer.	May 2017